



Fig. 1.



Fig. 2.

sional diagnosis of subacute bacterial endocarditis was made and penicillin was started. On June 24, 300,000 units of penicillin G were administered every three hours. The patient showed distinct clinical improvement, and the temperature dropped to normal in two days and remained normal during the rest of his stay in the hospital. His general condition and sense of well-being improved daily.

On July 8, petechiae 3 to 5 mm. in size were observed over the extremities and neck. They were purplish in color, hard in consistency and were associated with itching. On July 9 the patient developed on the face and dorsum of both hands tense bullae containing hemorrhagic exudates. This was accompanied by severe edema of the face, particularly marked in the infraorbital area. The impression was that this was a hemorrhagic bullous variant of an erythema multiforme-like reaction to penicillin, but since this patient had subacute bacterial endocarditis, and had been treated only fourteen days, the drug was continued another twenty-four hours, accompanied by 100 mg. of Pyribenzamine as the initial dose, and 50 mg. every three hours.

The next day the reaction became worse (Figs. 1 and 2). There was complete closure of both eyes and massive swelling of face, hands, and scalp. Although the pruritus had been controlled, the bullous lesions became very tense or ruptured to form erosive patches. At this time, penicillin was stopped (July 9), 50 mg. of Benadryl were given every four hours, instead of Pyribenzamine, and boric acid compresses were applied to the eyes and to the areas of the ruptured bullae. The following day his condition was improved and there was reduction in the periorbital swelling. During the active phase of the eruption, fluid from one of the bullae was removed and injected into the skin of an individual not sensitive to penicillin. Forty-eight hours after this intracutaneous injection of the blister fluid, the recipient received 300,000 units of penicillin G. A reaction characterized by erythema, edema and papulization became manifest at the site of the previous intracutaneous injection (a positive Urbach-Koengstein test—implying the passive transfer of tissue antibodies). Normal control blister fluid at another skin site on the recipient gave a negative reaction.

This patient continued to improve clinically insofar as his drug eruption was concerned. No bullae appeared after penicillin was stopped, the edema and bullae gradually subsiding. The patient was discharged on July 24 much improved.

Because of the inadequate course of treatment for this patient (he had received penicillin for only sixteen days) and because of the unusual reaction to the drug, he was followed in clinic and his further course noted. For a short period of time there was a slow progressive improvement but this was soon followed by a return of his

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COTTONSEED PROTEIN vs. COTTONSEED OIL SENSITIVITY

I. Background and Personal Experience

HARRY S. BERNTON, M.D.

Washington, D. C.

THE title of this symposium, "Cottonseed Protein vs. Cottonseed Oil Sensitivity," is misleading. There is no incompatibility between cottonseed protein and cottonseed oil. In nature, these substances exist in a symbiotic combination, as it were. Mere man comes along and disrupts their union. The consequent cleavage has given rise to a sharp difference of opinion among allergists concerning the allergenic properties of cottonseed oil in contradistinction to those of the defatted cottonseed meal.

At the outset, permit me to state my position. Sensitiveness to cottonseed flour or meal and to cottonseed oil are two distinct clinical entities. Sensitiveness to one does not connote sensitiveness to the other. Finally, we have shown that edible cottonseed oil is free of the allergen existent in the meal.

Let us now bring the background to the fore. Brown¹ in 1929 reported an incidence of 6 per cent of positive reactors to cottonseed protein: "thirteen out of a total of 214 definitely sensitive patients tested." Four of these thirteen patients, who reacted to cottonseed, were also tested "cutaneously with a drop of pure cottonseed oil, with negative results." Brown surmised that the cottonseed oil used in testing was probably so refined that all traces of protein had been removed. This opinion was reaffirmed by expert witnesses who testified at a public hearing before the Administrator of the Federal Security Agency, held at Washington, D. C., during November, 1947, and January, 1948.

In 1931, Bowman and Walzer,² who had contributed a chapter dealing with atopens and other excitants in one of the early textbooks on allergy, made the following assertions: "The active principle in cottonseed is probably a protein. . . . The oil of cottonseed contains active atopen and may

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therefore induce symptoms as an inhalant, ingestant, or contactant." This opinion has profoundly affected medical thought and practice. Thus, patients who were found sensitive to the extract of cottonseed meal were cautioned against the use of food products of which cottonseed oil was an ingredient. This is exemplified by statements made by Taub¹² in 1934. The opinion, "The oil of cottonseed contains active atopen and may induce symptoms as an inhalant, ingestant and contactant," is re-echoed. "It is almost impossible," he added, "to state all uses to which cottonseed and its products may be put or to determine all forms in which the active atopen principle may cause trouble to the hypersensitive patient." Taub enumerated thirteen sources of cottonseed as an ingestant and included Wesson oil and Crisco in the list.

In 1937, Rowe furnished interesting statistics on food sensitizations. In his table No. 30—the number of 1- plus, 2-plus, 3-plus, and 4-plus reactions to individual food allergens in 500 patients who gave one or more positive reactions—cottonseed does not appear. In his table No. 31—positive and negative cutaneous reactions to foods to which clinical sensitization existed in a series of 175 patients—there is reported one positive and one negative reaction with cottonseed. In his work, however, three cases of sensitiveness to cottonseed oil are described. Then comes a startling statement from Rowe: "I have recently demonstrated cottonseed allergen in Wesson oil."

Two years later, in 1939, Spies, Bernton and Stevens¹⁰ first announced the isolation of a protein allergenic fraction from the water-soluble constituents of cottonseed embryo. They designated the fraction CS-1. This fraction is composed of protein and polysaccharide. Subsequent investigations have firmly established the fact that the protein component is responsible for the specific allergenic activity of the meal. In the following year, these authors² described a series of experiments which justified the conclusion that the specific and exceedingly potent water-soluble allergen of the cottonseed embryo did not occur in refined cottonseed oil. In this study, patients highly sensitive to the cottonseed allergen, CS-1A, gave negative reactions to the refined, edible cottonseed oil on contact with the skin; on ingestion and on instillation into the conjunctival sac and upper respiratory tract. Cottonseed oil, in doses of two to three tablespoonfuls daily, was prescribed for five patients, and the quantities of the oil dispensed were, respectively: 100, 150, 200, 300, and 500 ml. In addition, three patients were given saltine crackers spread with a heaping tablespoonful of the hydrogenated cottonseed oil. One patient was provided with a one pound can of the hydrogenated oil, which was used liberally as a substitute for butter. The absence of ill effects was noteworthy. Finally, eight normal individuals received a single sensitizing injection of a cottonseed serum in a skin site on the upper arm. Six of the eight skin areas exhibited no detectable response following ingestion of cottonseed oil but reacted positively to the orally administered cottonseed allergen derived from the seed itself. The remaining two sites were negative.

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The attempt was also made to detect the presence of the cottonseed allergen in the refined oil. Three liters of the oil were passed twice in droplet form through a narrow column of 100 ml. of water. The water extract was thereafter concentrated to a volume of 15 ml. No nitrogen was found in the concentrated aqueous extract by the Kjeldahl micromethod, nor was nitrogen detected by the most sensitive qualitative test available.² Both cutaneous and intracutaneous tests were performed with the water extract on four of our cottonseed-meal-sensitive patients, with negative results. Two recipients, moreover, were sensitized with a cottonseed serum of high titer. The two passively sensitized sites yielded negative results when tested with the same aqueous extract of the oil.

The authors are careful in stressing the point that their findings are not submitted as evidence that clinical sensitiveness to refined cottonseed oil may not be encountered. Accordingly, Swineford's assertion that there is not a single authentic case of cottonseed oil sensitivity recorded in the literature is, indeed, challenging.³ Interestingly enough, Figley⁴ presented details of two cases suspected of specific sensitiveness to cottonseed oil. A follow-up study of these two cases, however, revealed an inconsistency in their reactions to the ingestion of samples of cottonseed oil and of other vegetable oils, submitted in a mask manner. Accordingly, Figley has become skeptical as to whether his cases are truly those of sensitiveness to cottonseed oil.⁵

The failure of cottonseed oil to provoke skin reactions, even in patients sensitive to cottonseed meal, has been noted by Brown, Figley, Mitchell, Loveless and by ourselves. Moreover, reagins for cottonseed allergens in the two alleged cases of cottonseed oil sensitiveness, recorded by Figley, were absent. Consequently, the diagnosis of cottonseed oil sensitiveness must be based on ingestion test. It is the only available criterion of sensitiveness to this particular derivative of cottonseed. Moreover, the ingestion test can be misleading unless it is designed and conducted in a manner to assure reliable and significant data.

In 1947, Spain⁶ wrote critically of what he regarded as inadequate food labeling. He protests, "The term 'vegetable' oil means little to the asthmatic highly allergic to cottonseed oil, but quite able to tolerate soy, peanut or corn oil." Cooke,⁷ in discussing allergy of the skin, lists twenty-four foods as potential causes of urticaria. Cottonseed oil is the last article of food enumerated. "Among these foods," he continues, "it is difficult to say which is the most important or to grade them as to their relative frequency in provoking reactions." By inference at least, Cooke and Spain recognize the existence of cases of sensitiveness to cottonseed oil in their practice.

Nevertheless, our search for a patient sensitive to cottonseed oil continued; and the opportunity to study an alleged case of sensitiveness to the oil in the person of a distinguished allergist was as welcome as it was revealing. The details of this investigation will appear in a future publication.⁸ It may not be amiss, therefore, to present a brief summary of our

findings. The patient was sure that all shortenings containing cottonseed oil caused abdominal discomfort—acute gripping pain and diarrhea. Canker sores, edema of lips and occasionally hives were other manifestations of his allergic reaction to cottonseed oil. He was confident he could differentiate cottonseed oil from corn oil with some discomfort. We were unable, however, to demonstrate by passive transfer tests the presence of reagins for water-soluble cottonseed protein or for cottonseed oil in his serum. Accordingly, the ingestion experiments in which our collaborator participated provided a noteworthy sequel to the serological study. Samples of vegetable oils, which included corn oil, cottonseed oil and olive oil were submitted in trial doses. Neither the subject nor the dispenser of the oils was informed of the composition of the individual samples until the close of the tests. Five of the fourteen samples contained cottonseed oil but in no instance were symptoms of distress provoked by ingestion of them. His failure to discriminate between cottonseed oil and corn oil became evident.

Assured and reassured by the results of the ingestion test, our collaborator is now enabled to partake of foods with cottonseed oil as an ingredient. To an allergist of mature clinical experience, we express our thanks for the demonstration of the importance of the "blind-fold" technique in the diagnosis of food allergy.

Our studies of the allergic phases of the cottonseed problem have extended over a period of ten years. The dietary restrictions, imposed upon the 6 per cent of the allergic population who are sensitive to cottonseed flour or meal, seem to us unwarranted in the light of the newer knowledge. Any attempt to avoid the ingestion of cottonseed oil presents difficulties—almost insurmountable. The culinary utilization of the oil embraces so many of our every day articles of diet, of which shortenings, salad dressings, potato chips, fried chicken, fried fish, canned sardines and tuna fish, bakery and candy products and oleomargarine are familiar representatives. At this point, it is important that we reiterate our former position: "Our findings are not submitted as evidence that clinical sensitiveness to refined cottonseed oil may not be encountered." We do insist, however, that the diagnosis of such sensitiveness be based on adequate data.

In this present restless and uncertain age, the psychosomatic aspects of allergic states are being stressed by clinicians. The biochemist is equally concerned when in allergic conditions the psyche is separated from the soma and especially the stoma.

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COTTONSEED PROTEIN vs. COTTONSEED OIL SENSITIVITY

II. A Case of Cottonseed Oil Sensitivity

THERON G. RANDOLPH, M.D., F.A.C.A., Chicago, Illinois
and

WILFRED N. SISK, M.D., Kalamazoo Michigan

BERNTON, Coulson and Stevens¹ and Figley² have recently reviewed the subject of sensitivity to edible vegetable oils with particular reference to the question of cottonseed sensitivity. They pointed out that allergists for the most part have made no distinction between sensitivity to cottonseed meal and cottonseed oil, and that it had been assumed by many that cottonseed oil contains sufficient traces of the highly potent cottonseed protein to cause allergic symptoms.

Bernton, Spies and Stevens² were the first to question this apparent relationship; they showed that the water-soluble active principle of cottonseed meal is not present in commercially available edible cottonseed oil or hydrogenated cottonseed oil and that patients who are clinically sensitive only to water-soluble cottonseed extractives may safely be spared the inconveniences of attempting to avoid cottonseed oil.

Although somewhat outside the scope of this particular presentation, our experience is in agreement with these fundamental observations of Bernton and his associates. We have no desire to enter this controversy, as reviewed by Figley³ and presented in detail by several witnesses appearing before the public hearings held under auspices of the Federal Food and Drug Administration for the purposes of establishing definitions and standards of identity for salad dressings.⁴

Our aim in this communication is to cite evidence in favor of the existence of clinical sensitivity to cottonseed oil. In our cases of cottonseed oil sensitivity, to be presented herewith, there was no evidence of sensitivity to cottonseed protein as determined by the existence of positive skin tests with the water soluble fraction of cottonseed.

Case 1.—A physician, aged thirty-eight, had been subject to perennial nasal and sinus symptoms since 1927, unexplained chronic fatigue since 1928 and intermittent bouts of gastrointestinal symptoms, conjunctivitis and urgency and frequency of urination for the past decade. For the past six years he had complained of chronic muscle soreness and intermittently painful joints, although there had been no evidence of swelling, limitation of motion or x-ray abnormalities of the involved joints.

He was characteristically awakened in the middle of the night by insomnia and epigastric distress. All symptoms were accentuated on arising in the morning. He experienced a flare of fatigue, nervousness and abdominal distress beginning between two and three hours after each meal. He learned the most satisfactory manner by means of which temporary relief could be obtained from these symptoms was to eat additional food at the time of their onset. The satiation of this voracious ap-

Presented at the Fifth Annual Meeting of the American College of Allergists, April 14-17, 1949, Chicago, Illinois.

Dr. Randolph is an instructor in medicine, Northwestern University Medical School.

Dr. Sisk is with the Upjohn Company, Kalamazoo, Michigan.

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petite for interval feedings resulted in the development of moderate obesity and the apparent inability to follow a reduction type of diet. He also learned that foods containing corn were most effective in bringing about this temporary degree of relief.

The patient was aware that peaches, oranges, coffee, chocolate and Coca-Cola increased his gastrointestinal distress, and the ingestion of lemon or tea was followed by increased irritability and nervousness.

A diagnosis of hypoglycemia had been suspected repeatedly, but this interpretation of his symptoms had not been confirmed by diagnostic laboratory data. Although he frequently had a purulent discharge from the prostate, conjunctivae and sinuses, chronic infections involving these areas could not be demonstrated.

Aside from moderate obesity and pale, boggy nasal mucous membranes, his physical examination was within normal limits.

An allergic study revealed skin test evidence of sensitivity to house dust, feathers and orris root. A scratch test with cottonseed extract was negative; other skin tests with foods were not performed.

An individual food test with corn (according to Rinkel's technique⁹ as modified slightly by Randolph and Rawlings⁸) was followed by a sharp immediate increase of his fatigue and gastrointestinal distress. A similar test with potatoes was followed in thirty minutes by the chilliness, sneezing and rhinorrhea. Sensitivity to chocolate and grape was determined on the basis of similar direct evidence. Individual food tests with other major foods were not associated with reactive symptoms.

In spite of the maintenance of inhalant therapy and the avoidance of foods incriminated at this stage of the diagnosis, he had only partial relief of his chronic allergic symptoms.

Sensitivity to cottonseed was suspected during the course of avoiding milk prior to performing an individual food test with this food, as he felt decidedly worse during this period in which he had materially increased his intake of home-made mayonnaise prepared from Wesson oil. His suspicion of cottonseed sensitivity was further aroused when he observed that his headache, fatigue and general irritability were accentuated following meals containing cottonseed oil. The individual ingredients of the home-made salad dressing were then omitted four days each and tolerated when returned to the diet with the sole exception of cottonseed oil. The trial ingestion of 15.0 c.c. of Wesson oil was followed by the prompt occurrence of headache and abdominal distress. He reported marked improvement following the avoidance of cottonseed-containing products. He then returned cottonseed oil to his diet in the previously ingested amounts, continuing his other dietary measures as outlined, and on the second day reported the recurrence of frequent to continuous headaches, general lassiness and marked fatigue.

He was then instructed in the absolute avoidance of all cottonseed oil for four days prior to the performance of an individual food test with 15.0 c.c. of commercial Wesson oil. Ten minutes following the test feeding, he developed a sharp headache coincident with the complaint of a "rock-like" sensation in the abdomen. Variations of the total leukocyte counts following this test are shown in Figure 1. Residual weariness to an extreme degree persisted for an additional twenty-four hours.

He then avoided all sources of cottonseed oil, eating only food prepared in his own home. He remained free of allergic symptoms under these circumstances, but on each occasion that he ate away from home for a few consecutive meals he had a recurrence of his headache and fatigue within one to three days even though he attempted to avoid cottonseed and other incriminated foods. On several different occasions he developed a recurrence of cramping sensations in his leg muscles and other described constitutional symptoms following the ingestion of food subsequently learned to have been prepared with cottonseed oil.

It should be stated that similar symptoms were known to follow the ingestion of corn. However, it has been clearly shown that the test or inadvertant ingestion of

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cottonseed oil in the absence of corn intake has repeatedly produced the symptomatology in question.

After a year of avoiding cottonseed except for an occasional contact incident to attending medical meetings, he has developed a slight degree of tolerance to cottonseed oil in that a single feeding in the amounts obtained by chance may now be taken

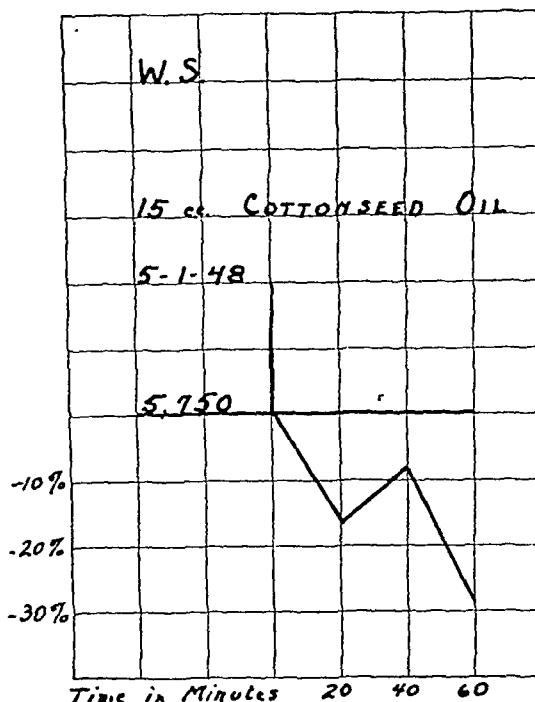


Fig. 1. Variations in the total leukocyte counts following the experimental ingestion of 15.0 c.c. cottonseed (Wesson) oil.

without the recurrence of symptoms. The ingestion of small amounts in repeated feedings still results in the redevelopment of headache, fatigue and irritability. The trial ingestion of cottonseed meal has not been attempted.

It is of further interest that he has had no joint symptoms during the past year except after the use for a week of a brand of bread known to have been corn-free and thought to have been made with lard but subsequently found to have contained cottonseed oil.

Case 2.—E. R., a housewife, aged fifty-four, had been subject to severe headaches for fifteen years, during the past decade of which she had complained of constant headaches, dizziness and myalgia of the posterior cervical muscles and upper back. When first seen in 1946, she also complained of a debilitating degree of weakness, chronic dermatitis of her hands and alternating constipation and diarrhea.

Her clinical history of house dust sensitivity was confirmed by positive skin tests with house dust extract, specific therapy having been helpful in controlling a part of her symptomatology. She was shown to have a widespread allergic response to foods, indicated by the precipitation of acute clinical reactions following the experimental ingestion of several articles of the diet in accordance with the technique of the individual food test.^{8,9}

The maintenance of house dust therapy, the avoidance of silk and incriminated

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foods, and the use of other foodstuffs on a rotating schedule¹⁰ were effective in relieving her chronic symptoms for a period of several months.

In early 1948 she reported a gradual recurrence of symptoms in spite of strict adherence to her previously effective environmental and dietary control. She was subjected to several other individual food tests including cottonseed oil. Following the

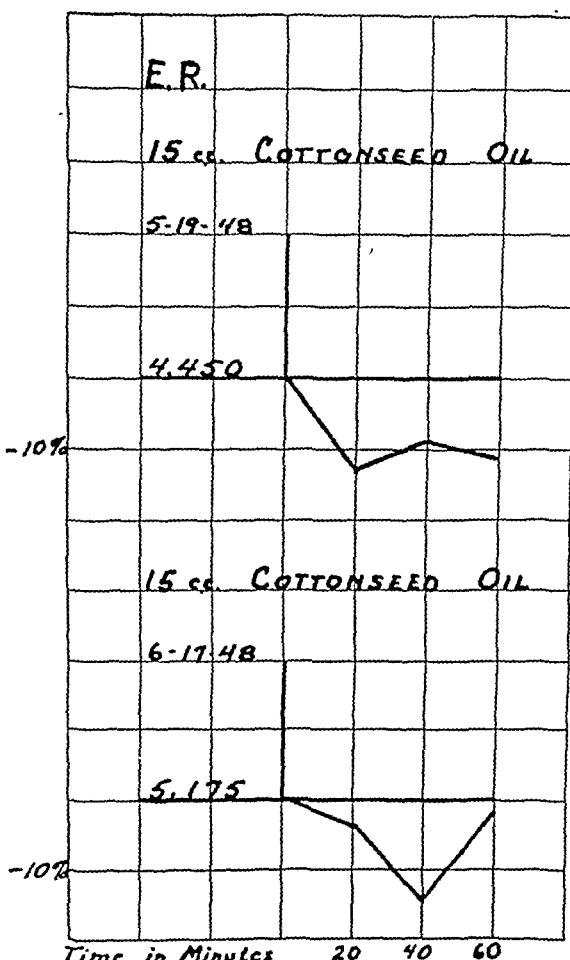


Fig. 2. Variations in the total leukocyte counts on each of two occasions following the experimental ingestion of 15.0 c.c. cottonseed (Wesson) oil.

avoidance of cottonseed in all forms for four days she ingested 15.0 c.c. of Wesson oil experimentally. Thirty minutes later she complained of marked sleepiness and at forty minutes developed a mild frontal headache; these symptoms became progressively severe during the remainder of the day, in association with the development of drawing, aching pains in the lower back, and extreme fatigue. The morning following the cottonseed oil test, her back was so stiff and sore that it was necessary to be assisted in arising from bed. She remained extremely constipated for the three following days.

Two months later she was again subjected to a cottonseed oil test, again taking 15.0 c.c. of Wesson oil fasting, after having avoided cottonseed oil since her previous test. She noticed the onset of yawning and sleepiness beginning thirty-five minutes later; this was followed shortly by nausea, abdominal distress and tautness, pulling and drawing sensations of the posterior cervical muscles. Ninety minutes after the

test ingestion of cottonseed oil she developed a headache. During the afternoon of the test she complained of nausea, abdominal cramps and passed several diarrheic stools. Her gastrointestinal symptoms and extreme fatigue persisted for an additional two days.

During the past year she has found it necessary to avoid cottonseed oil completely, for each of several times that it has been ingested in small amounts inadvertently she has had a recurrence of headache, myalgia and fatigue. If taken in a larger quantity she experienced abdominal cramps and diarrhea.

Variations in the total leukocyte counts following these two tests are illustrated in Figure 2.

DISCUSSION

In addition to well-recognized allergic manifestations, both patients presented the symptoms of chronic fatigue and myalgia, first recognized as of allergic origin by Rowe^{12,13} and subsequently reviewed by one of us.^{6,7} The second patient also had joint manifestations highly suggestive of early arthritis which responded to allergic management in a manner similar to those recently reported by Zeller.¹⁵ Both individuals had the typical timing of their chronic symptoms at specific times of the day indicative of the masked symptomatology of chronic food allergy as described by Rinkel.¹¹

We believe that the data herewith presented may be interpreted in only one way, namely, that these two individuals are clinically sensitive to cottonseed oil as it is found in commercial foods.

The question of whether the symptoms in these cases might be explained on the basis of corn oil as an inadvertent contaminant of cottonseed oil must be raised in view of the well-known commercial practice, in at least certain oil refineries, of employing the same equipment in refining both cottonseed oil and corn oil, and the fact that both of these patients were clinically sensitive to corn. This question has been discussed with technicians familiar with refinery processes. There was agreement that while there might be such a contamination in an occasional lot, this would certainly not be true in the vast majority of cottonseed oil specimens. The consistency with which the ingestion of cottonseed oil has been followed by the development of clinical symptoms in these patients would make it highly improbable that the symptoms were caused by the ingestion of corn oil as a contaminant.

Doubt has been expressed in certain quarters as to the allergenicity of refined vegetable oils. It is agreed that the oil fractions of foods cause allergic symptoms less frequently than other refined food products and that many patients sensitive to whole foods are able to tolerate specific refined oils in cumulative feedings without developing clinical responses. There are numerous instances, however, in which refined vegetable oils are known to produce allergic symptoms. Duke⁸ was the first to point out the allergenicity of soy bean oil, and Rowe¹⁴ has incriminated cottonseed,* corn, peanut and olive oils. In our clinical experience, the experimental ingestion of

*Dr. Albert H. Rowe has recently informed us that his case of allergy to cottonseed oil also failed to show skin reactions to cottonseed protein. He has also recently re-established the fact that the ingestion of cottonseed oil continues to cause allergic symptoms in this patient.

corn oil and peanut oil have been shown to cause allergic reactions in certain instances in which other fractions of the same foods were known to be allergenic. Although we have tested several patients with skin test and clinical evidence of sensitivity to cottonseed meal, as yet we have not been able to induce allergic responses when these same individuals were experimentally fed commercially available cottonseed oil. Our experience in this respect confirms the statements of Bernton, and associates^{1,2} Figley⁵ and others.

It should be re-emphasized that the cases of apparent sensitivity to cottonseed oil, herewith reviewed, differ from those previously reported in that these individuals react with allergic manifestations following the ingestion of cottonseed oil but fail to give positive skin tests with extracts of cottonseed protein.

The incidence of this type of cottonseed sensitivity would seem to be relatively rare as we have encountered only two cases in approximately seventy-five patients who have been subjected to individual food tests with cottonseed oil (Wesson oil). The possibility of cottonseed oil sensitivity was suspected only in those patients who continued to have unexplained allergic symptoms after two months of diagnostic food studies, during which time all previously incriminated articles of the diet had been avoided.

In each instance all cottonseed products were scrupulously avoided for a period of four days prior to the experimental ingestion of cottonseed oil. Care was taken to conduct the preliminary period of specific avoidance at a time when the patient was able to prepare and eat all meals at home. The technique of the individual food test is that described by Rinkel⁹ and modified slightly by Randolph and Rawling.⁸ In the two positive cases it may be observed that the criteria for the existence of specific sensitivity were based primarily on the precipitation of allergic symptoms, although in each instance there was an associated decrease of the total leukocyte counts (Figs. 1 and 2). The significance of the variation of the total leukocyte levels in the individual food test has been discussed elsewhere.⁸

SUMMARY

Two cases of cottonseed oil sensitivity in the absence of sensitivity to cottonseed protein, as determined by negative skin tests with extracts of cottonseed, are reported.

In both instances, the experimental or inadvertent ingestion of cottonseed oil as encountered in commercially available foods has been shown to result in the production of allergic symptoms.

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COTTONSEED PROTEIN vs. COTTONSEED OIL SENSITIVITY

III. The Atopen Content of Cottonseed Oil

ROBERT STERLING McGRATH, M.D., F.A.C.A.

Washington, D. C.

THE purpose of this investigation was to determine whether the atopen of cottonseed could be detected in crude cottonseed oil, or in any of the various stages of refinement of the oil, and if so, whether the refining processes altered the atopen content.

In the present study, samples of cottonseed oil were obtained from each of the stages of commercial refinement. Extracts were prepared by various methods from each of these oil samples, suitable for intracutaneous testing. The presence of the cottonseed atopen was then detected in these extracts by the Prausnitz-Kustner technique, using a high titered cottonseed serum of known strength.

DESCRIPTION OF COTTONSEED OIL SAMPLES

The cottonseed oils used in this investigation were specimens from each of four stages of commercial refining. The samples were supplied by the National Cottonseed Producers' Association, through courtesy of Dr. Henry Stevens. This material consisted of four samples which were labeled as follows: Oil 1—crude oil; oil 2—alkali refined oil; oil 3—bleached oil; oil 4—deodorized oil. In addition, a fifth sample—Wesson oil—was obtained by the purchase of an original container on the open market, and so labeled.

PREPARATION OF EXTRACTS

Extracts suitable for intracutaneous testing were prepared from these five samples of cottonseed oil by various methods. Different proportions of oil, chloroform and diluent, 5/10 per cent phenol in normal saline, were agitated and allowed to stand for varying periods. The water soluble fraction was sterilized and used for testing. The procedures were tabulated in Table I. A summary of this table revealed that the most potent extracts were obtained when two parts each of the respective oil and chloroform were added to one part diluent, agitated fifteen minutes, and allowed to stand forty-eight hours at 10° C.

STANDARDIZATION OF SERUM

The serum used in the present study was obtained from a patient, M.C., who presented a marked clinical sensitivity to cottonseed. This serum was

From the Division of Allergy, Department of Medicine, Garfield Memorial Hospital, Washington, D. C.
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TABLE I. PREPARATION OF EXTRACTS

Extract Number	Oil Sample	Oil c.c.	Chloroform c.c.	Diluent c.c.	Mixing Time Minutes	Extracting Time Hours	Sterilization	Extract Activity
1*	1	10	50	50	15	12	S	Moderate
2*	1	10	50	50	15	24	SS	Moderate
3*	1	10	35	35	15	12	SS	Moderate
3A**	1	10	35	35	15	12	S	None
4***	2	10	50	50	15	24	T	Slight
4A****	2	10	50	50	15	24	T	None
5	1	10	50	50	25	72	T	None
6	3	10	20	20	30	12	T	Slight
7	4	10	20	20	30	12	T	Slight
8	2	10	20	20	60	12	T	Slight
9	3	10	20	20	60	12	T	Slight
10	4	10	20	20	60	12	T	Slight
11	5	20	20	10	10	12	SS	Moderate
14	2	20	20	10	15	48	SS	Marked
15	4	20	20	10	15	48	SS	Moderate
16	2	30	20	5	10	12	SS	Moderate
17	3	30	20	5	10	12	SS	Moderate
18	4	30	20	5	10	12	SS	Moderate
19	5	30	20	5	10	12	SS	Moderate

*Formed 3 fractions after agitation.

**A second aqueous fraction collected from Ext. 3 on standing an additional 12 hours.

***Formed 2 fractions after agitation; aqueous fraction formed in 12 hours.

****Extract 4, in part, was concentrated to 4 c.c. by evaporation by fanning.

S Sterilized by Seitz filtration.

T Sterilized by covering with toluol and allowing to stand 72 hours at 10° C.

standardized by the serum dilution method of Coca and Grove,³ and the atopen dilution method of Levine and Coca.⁴

Serum Dilution Method.—Serial dilutions were made with M.C. serum in normal saline, as follows: 1:4; 1:16; 1:256; 1:1024; 1:4096. Skin sites on two normal subjects were sensitized with these respective dilutions. Refractoriness of the site was eliminated by allowing an interval of four days between sensitizing and testing. The subject was instructed *not* to ingest cottonseed in any form.⁵ Nonspecific cutaneous reactions were ruled out by testing some of the sensitized sites with diluting fluid. The remaining sensitized sites were tested with about .02 c.c. each of a cottonseed extract containing .01 mg. of total N per c.c. It was found that this serum transferred a cottonseed sensitivity in a dilution of 1024, but not of 4096.

Atopen Dilution Method.—M.C. serum in undiluted form was used to sensitize about six skin sites each on two nonatopic subjects. Nonspecific cutaneous reactions and refractoriness of the site were ruled out as before. The subject was instructed *not* to ingest cottonseed in any form. A standardized cottonseed extract was serially diluted to contain respectively .000,01, .000,001, .000,000,1 and .000,000,01 mg. of total N per c.c. and tested on these sensitized sites. It was found that the atopen of cottonseed was definitely detected in a dilution containing .000,001 mg. of N per c.c. Testing with the next greater dilution gave doubtful reactions, and testing with further dilutions were negative. The result of this standardization showed that the atopen of cottonseed was definitely detected in an extract containing .000,001 mg. of total N of cottonseed per c.c. by use of this serum and with this technique.

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TABLE II. PASSIVE TRANSFER TESTS
WITH EXTRACTS PREPARED FROM COTTONSEED OILS

Subject	Age	Extract	Oil	Reaction Sensitized Site	Reaction Control Site	Degree of Reaction
1	38	1	1	SI—	6	2
2	42	1	1	SI+	10	8
2	42	13	1	SI+	10	8
3	35	4	2	SI	8	0
4	30	7	4	SI	8	4
5	17	9	3	Neg+	2	0
5	17	10	4	NegSI	4	4
6	38	14	2	SI+	10	4
6	38	15	4	SI+	10	4
7	21	11	5	NegSI	4	2
8	44	15	4	SI+	10	4
9	24	14	2	SI+	10	0
10	25	11	5	SI+	10	0
11	24	14	2	SIMod	12	0
11	24	14	2	SIMod	12	0
12	20	14	2	SI—	6	0
12	20	15	4	NegSI	4	0
12	20	11	5	SI	8	0
13	25	16	2	NegSI	4	0
13	25	17	3	Neg+	2	0
14	20	17	3	NegSI	4	2

Degrees of Reaction with Numerical Equivalent

Reaction*	Neg	Neg +	NegSI	SI—	SI	SI +	SIMod	Mod	Mod +	ModMkd	Marked
Number	0	2	4	6	8	10	12	14	16	18	20

*Reaction—Combined evaluation of wheal, erythema and pruritus.

DETECTION OF COTTONSEED ATOPEN IN UNKNOWN EXTRACTS

The atopen content of the extracts prepared from the samples of cottonseed oil was next determined by use of this high titered serum by the Prausnitz-Kustner technique, but according to the refinements of indirect testing described by Walzer.^{2,6} The subjects selected were young, non-atopic individuals with normally reacting skins.⁷ The reactivity of the skin of each subject was determined by preliminary direct intracutaneous tests with extracts of ragweed, timothy, horse dander, and house dust. These subjects were next sensitized with undiluted M.C. serum in multiple sites, placed transversely across the upper outer aspect of the arm, 2 inches apart.¹ Each site was encircled with fountain pen ink to insure its future location. The subject was instructed *not* to ingest cottonseed in any form. Refractoriness was eliminated by an interval of four days between sensitizing and testing. Nonspecific reactions were ruled out by testing some of the sensitized sites on each subject with saline and extracts of corn and peanut. The remaining sensitized sites on each subject were intracutaneously tested with about .01 c.c. of the various extracts prepared from the samples of cottonseed oil, and a control test of the same size and with the same extract was injected into the unsensitized skin about 3 inches distal to the sensitized site. The reactions were noted in thirty minutes. A test was considered positive when there was an excess of reaction on the sensitized site when compared with the control. Tests were recorded in terms of ten degrees of positive reactions. To facilitate graphic comparison a number was assigned each degree of reaction. The final reaction was the numerical difference between the degree of reaction on the sensitized and controlled sites (Table II).

COTTONSEED SENSITIVITY—McGRATH

TABLE III. COMPARING THE ATOPEN CONTENT
OF CRUDE AND REFINED COTTONSEED OILS

Subject	Age	Extract	Oil	Reaction Sensitized Site	Reaction Control Site	Degree of Reaction
6	38	14	2	SI+	10	4
9	24	14	2	SI+	10	0
11	24	14	2	SI Mod	12	0
11	24	14	2	SI Mod	12	0
12	20	14	2	SI-	6	0
6	38	15	4	SI+	10	4
8	44	15	4	SI+	10	4
12	20	15	4	NegSI	4	0

Degrees of Reaction with Numerical Equivalent

Reaction*	Neg	Neg +	NegSI	SI-	SI	SI +	SI Mod	Mod	Mod +	ModMkd	Marked
Number	0	2	4	6	8	10	12	14	16	18	20

*Reaction—Combined evaluation of wheal, erythema and pruritus.

Twenty-one tests were made on fourteen subjects with ten different extracts, prepared from the five samples of oil. A summary of this table revealed that the crude oil had three extracts prepared from it, which were tested on three subjects, each of which gave a slight but definite positive transfer, with a reaction value of about 3. The alkali refined oil was tested on seven subjects, by two extracts. Each test gave a definite positive transfer with a reaction value of 9. The deodorized oil had two extracts prepared from it, which were tested on three subjects. The reaction value was about 2. The bleached oil had three extracts prepared from it which were tested on five subjects. Each test was positive, with a reaction value of about 5. Wesson oil had one extract prepared from it which was tested on three subjects. Each test was positive with a reaction value of 6. These results showed that the atopen of cottonseed was detected in the crude oil, and also in the various stages of processing the oil.

EFFECT OF REFINING PROCESSES ON ATOPEN CONTENT OF THE OIL

To determine whether the refining processes altered the atopen content of these oils, the alkali refined oil was compared with the refined bleached oil by the same technique. Extracts 14 and 15 were used in this comparison, both of which were prepared by the same method. The results were tabulated in Table III. Examination of this table revealed that the crude alkali refined oil, represented by extract 14, was tested on four subjects. Each transfer test was positive, with an average reaction value of about 10. The refined bleached oil, represented by extract 15, was tested on three subjects. Each test was positive, and the average reaction value was about 6. From these results it was apparent that the refining processes of cottonseed oil may diminish the atopen content of cottonseed slightly, but does not destroy the active principle.

SUMMARY AND CONCLUSIONS

1. The atopen of cottonseed was detected in the samples of crude and refined cottonseed oil by use of this serum and with this technique.

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COTTONSEED PROTEIN vs. COTTONSEED OIL SENSITIVITY

IV. An Objective Approach to the Diagnosis of Food-Allergy as Applied to Cottonseed Atopy

MARY HEWITT LOVELESS, M.D.
New York, New York

IT is common knowledge that an *adequate* amount of allergen must be present in a given exposure for the allergic patient to develop symptoms, and that the minimal requirement varies with the individual. It is surprising, therefore, that so little information is available concerning what might be called a "minimal provocative dose" of an allergen. Physicians have preferred to judge their subjects' susceptibilities by means of tests carried out in the skin, even though it may not participate in the clinical disorder. The reasons for this are, no doubt, the ready availability of the dermis and the difficulty of arranging for uniform, graduated exposures to such allergens as pollens. It appealed to the author that food allergy could be evaluated through ingestion-tests carried out with graded doses of chemically standardized, food extract. The need for some such test became apparent during hearings before the U. S. Food and Drug Administration in 1947 and 1948, when the labeling of salad oils and dressings was discussed with particular reference to cottonseed as an allergen.¹ Although the expert witnesses agreed that this seed is highly allergenic, both by clinical and cutaneous tests, no one could state whether the small residue of protein in refined cottonseed oil is theoretically adequate to disturb the seed-allergic consumer.

In view of this situation, the present investigation was instituted in order to determine the tolerance of four cottonseed allergic adults for ingested cottonseed extract. Since it was desirable to relate the new procedure to conventional tests described in the literature, cutaneous, conjunctival and serological methods were also applied concurrently in such a manner as to elicit threshold responses. Having thus determined the minimal provocative requirements by various routes, we were in a position to establish a ratio between ingestive and other tissue tolerances, thereby endowing the latter tests with clinical significance. Furthermore, one could now evaluate the possible allergenic contamination of the oil by the performance of cutaneous and ingestion tests with the oil and its aqueous washings, any positive findings being matched against reactions obtained with known amounts of standardized extract.

MATERIAL AND METHODS

Patients.—Three healthy women, in their third and fourth decades, and one man in his twenties proved to be highly sensitive to the water-soluble

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From The New York Hospital and the Department of Medicine, Cornell University Medical College, New York, N. Y.

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constituents of cottonseed by clinical history and by several specific tests. Three of the group were also hypersensitive to pollens whereas the fourth was nonallergic except for a cutaneous reactivity toward house dust. Their histories are briefly recorded below.

duV.—This woman promptly develops itching and edema of her lips, tongue and throat after eating certain brands of doughnut, rolls and coffee-cake. She once exhibited a spectacular series of allergic reactions after tasting candy which was later found to contain a trace of cinacoa, or cottonseed flour. Within a few minutes, tingling and edema were noted in the mouth and throat; generalized urticaria soon occurred, followed by acute rhinitis, wheezing, nausea, vomiting and abdominal colic. She is clinically allergic to grass pollens as well as to cottonseed.

Sen.—Within fifteen minutes after eating a certain brand of white bread sold by a chain grocer, or certain kinds of doughnut, this woman regularly develops bronchial asthma. Upon nearing a couch upholstered with crude cotton wadding, she wheezes and becomes mildly dyspneic. During a course of immunization, she became violently asthmatic within half a minute after receiving a minute dose of cottonseed extract on several occasions. Indeed, her skilled allergist abandoned this form of therapy because of her extreme intolerance.

Woo.—Certain cookies, doughnuts, and breads provoke allergic dermatitis. Proximity to a couch upholstered with crude cotton padding results in wheezing. Therapeutic injections with cottonseed extract have produced generalized urticaria, marked asthma and hay fever within ten minutes on several occasions.

Sac.—This man does not appear to be as intensely sensitized toward cottonseed as the others, but has noted that he wheezes quite badly within ten minutes after lying on a cotton mattress. The ingestion of certain cookies and doughnuts leads to nausea.

All four subjects tolerate foods shortened with or fried in cottonseed oil or hydrogenated oils, as well as salad dressings made with the seed oil.

Tests.—Conjunctival, intracutaneous and scratch, serological.

After ether-defatted cottonseeds had been extracted in alkaline saline solution, the supernate was standardized on the basis of its phosphotungstic-acid-precipitable nitrogen, one-tenth milligram of nitrogen representing 10,000 "protein" nitrogen units (P.N.U.). A series of two-fold dilutions was prepared for testing purposes. The threshold response was then elicited in the eye of each patient by means of graded strengths of extract which were successively dropped into the conjunctival sac from a 26-gauge needle at five-minute intervals until slight reddening and itching were pro-

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duced.² The same preparations were used to provoke threshold responses in the skin, 0.02 milliliter being introduced intracutaneously in graduated strengths and in duplicate. For scratch tests, a series of incisions about 1 milliliter long and 3 inches apart were made with a fine hypodermic needle along the flexor surface of each forearm. Appropriate strengths of extract were applied to these until the threshold reaction appeared. In the case of the oil, not only was this product rubbed gently into similar scratches, but so also were washings derived by shaking a large measure of this oil with one-tenth or one-sixtieth its volume of physiological saline.

The Prausnitz-Kustner, or indirect cutaneous, test was done in the usual manner; viz., 0.1 ml. of serum was intracutaneously injected into normal skin and the site was injected after twenty-four hours with .03 ml. of extract, the strength of which was just adequate to provoke an approximately maximal response.

In other sensitization experiments, a series of tubes was set up with a constant measure of serum and increasing strengths of cottonseed extract. Sites of normal skin were then injected with these serum-allergen combinations, to be tested next day with more antigen (.03 ml. of 10-unit extract). Any sites responding to this secondary test had obviously not been desensitized by the amount of antigen included in the original mixture. The first unresponsive site provided the index to the neutralization requirement for the serum in question.

Ingestion Tests.—Cottonseed extract. Before this test, the patient was told that he would be given either diluent or diluted cottonseed extract to swallow but would not learn the true identity until the experiment had been concluded. When the testing material was seed extract, 100-unit material was first tried, a measure being placed on the tongue from a 1 ml. syringe. In thirty minutes 1000-unit solution was employed and finally, if necessary, 10,000-unit extract. Each dose of one ml. or less was swallowed with the aid of water taken from a glass. The test was interrupted when definite allergic symptoms developed.

The procedure was similar when the oil of cottonseed, or a control material such as corn oil, was to be tested by ingestion, the only exception being that the entire volume was administered in one feeding since little or no reaction was to be expected.

FINDINGS

The results of the threshold tests are summarized in Table I, the provocative doses being expressed in terms of "protein" (P.N.) units of phosphotungstic-acid-precipitable nitrogen. Table II gives the equivalent in micrograms of precipitable nitrogen. It also indicates the ratios found when the threshold level revealed by ingestion was divided by that determined through tests of the eye, skin or serum.

TABLE I. COMPARISONS BETWEEN AMOUNT OF COTTONSEED EXTRACT REQUIRED
AND BY VARIOUS OTHER ROUTES
AND BY PHOSPHOTUNGSTIC-ACID PRECIPITABLE NITROGEN
Expressed in Units of Phosphotungstic-Acid Precipitable Nitrogen
Transfer Table

TABLE I. COMPARISONS BETWEEN AND BY VARIOUS EXTRACTS Expressed in Units of Phosphotungstic-Acid Precipitants								
Cate-	Conjunctival Test			Intracutaneous Test			Scratch Test	
	Ingestion Test	Conjunctival Test		Amount* in units	Indirect Skin Test			
		Strength** in units	Amount* in units		Strength** in units	Amount* in units		
Chu	1.28	5	0.09	0.000,035	0.000,000,7	0.0047	2.5	
V	2,000	7½	0.14	0.000,008	0.000,000,2	0.0047	1.0	
Sen	1,000	20	0.37	0.000,032	0.000,006	0.156	5.0	
Woo	10,000	100	1.11	0.000,300	0.000,006	1.25	100.0	

* Actual amount invested per mil.

TABLE II. COMPARISON
... Expressed in Microgramme

Acetated monofilament available in 20m

duV.—Within several minutes of swallowing 0.1 ml. of extract containing 1280 P.N. units per ml., this woman developed slight sneezing and pruritus of her left lower lid. Thirty minutes after the first dose, she was given the same volume of 10,240-unit extract which shortly led to marked itching of the mouth and throat, flushing of the face and neck, and slight nausea. Her minimal requirement was assumed to have been met by the first ingestion, namely, 128 P.N.U. or 1.28 micrograms of precipitable nitrogen.

When increasingly strong extract was instilled into the conjunctival sac at five-minute intervals, a beginning erythema and pruritus of the eye were produced after extract containing 5 units per ml. had been employed. Since a fully rounded drop from a 26-gauge needle contains $1/54$ of a ml., the actual amount instilled in this threshold test was $1/54 \times 5$ or .0925 unit. When this figure in micrograms was divided into the amount required for the ingestion response, it appeared that 1400 times more antigen was needed for the clinical than for the conjunctival reaction (Table II).

An even greater difference existed between the ingestion requirement and the allergen needed for the intracutaneous response. Here extract containing only .000,035 P.N. units per ml. excited the minimal reaction when injected in a volume of .02 ml. The actual provocative dose was, therefore, $1/50$ of this figure, or 0.000,000.7 units. Table II reveals that by ingestion, 183 million times more had to be taken for a threshold response.

When serological studies were carried out in sites of normal skin which had been sensitized with 0.1 ml. of serum, it was found that much larger quantities of cottonseed extract than those referred to above had to be injected to elicit the first nearly maximal response, 0.156-unit extract proving effective. Even here, however, the requirement was $1/27,000$ of the ingestion test. To exhaust the serum of its sensitizing capacity, cottonseed extract had to be added to it in the proportion of 20 units to 1 ml. of serum. Hence, approximately one-sixth as much seed nitrogen was required for neutralization of serum reagins as for the precipitation of symptoms by the oral route.

As anticipated, the strength of extract needed for a positive scratch-test proved to be relatively great in comparison with any other tissue test. Extract containing about $1/50$ the ingestion dose produced the threshold response in *duV.*

In the case of the other three patients, differences of a comparable order of magnitude were found to exist between the clinical and the other provocative doses. This will be made clear by the over-all ranges listed at the bottom of Table II. These ratios of comparison between ingestive and other thresholds show that the passive-transfer neutralization requirement was relatively great, from six to 300 ingestion doses being required to exhaust 1 ml. of serum. The ratios were larger for the other tests in the following order: the scratch test, the indirect skin test (Prausnitz-Kustner), the conjunctival, and finally the intracutaneous method. It was sur-

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**TABLE III. ESTIMATE OF MAXIMAL* ALLERGEN CONTENT OF COTTONSEED OIL
By Scratch Tests with Cottonseed Extract and Washings from Oil**

Name	Ingestion Dose of Extract (in PNU)	Scratch Test Dose with Extract (in PNU/ml)	Extent of Concentration by Washing	Estimated Allergen Content of Oil (in PNU/ml)	Estimate of Volume of Oil Containing Ingestive Dose (in liters)
duV	128	2.5	60-fold	<0.04**	>3.2†
Sen	2,000	1.0	10-fold	<0.1	>20.0
Woo	1,000	5.0	60-fold	<0.08	>12.5
Sac	10,000	50.0	60-fold	<0.8	>12.5

*All scratch-tests with the oil and its washings were negative.

**The figure obtained when the scratch-test dose with extract was divided by concentration of washing.

†The figure obtained when the above result was divided into the ingestion dose determined for the patient.

Example: $2.5 = .04$ units of N; $128 \div .04 = 3,200$ ml. of oil.

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prising to learn in this way that millions to billions of times more nitrogen was tolerated by the oral route than by the endermal test.

Having determined the concentration of allergen required for the minimal scratch-test response, we were in a position to evaluate any activity in the seed oil. However, no positive responses could be elicited by scratch-testing with the latter, so that it became necessary to concentrate its water-soluble contaminant by means of small, saline washings. Such washings likewise failed to elicit more than suggestive erythemas. One was forced to conclude, therefore, that any active allergen remaining in the oil was present in amounts so small as to have no practical significance for the allergic consumer. The theoretical volume that could be tolerated orally by our patients was roughly estimated for the oil as follows:

The first patient gave no response to scratch-test with a washing obtained from 60 volumes of oil (Table III). This negative result indicated that fewer than 2.5 P.N. units per ml. must have been involved, since she had been found capable of reacting to seed extract in this concentration. Assuming that thorough shaking had removed all the water-soluble activity from the oil, there must have been fewer than 0.04 units per ml. in the unwashed oil ($1/60$ of 2.5 units). Carrying such calculations further, it was estimated that the patient could consume at least 3.2 liters of oil without obtaining enough of the water-soluble allergen to give her clinical symptoms. The figure, 3.2 liters, was obtained by dividing 128 units, her ingestive requirement, by .04 units per ml.

The second patient was found to be inordinately responsive by scratch-test as compared to ingestion. Her ingestion-scratch ratio was 2,000, whereas for the other patients this fell between 50 and 200 (Table 2). In spite of her capacity to detect minute amounts of seed by scratch-test, neither the oil nor washings prepared from 10 volumes led to any erythema in her skin. Consequently the oil was assumed to contain fewer than 0.1 unit per ml., and the conclusion was drawn that the patient could ingest 20,000 ml. of oil before approaching her clinical provocative dose of 2000 units of seed nitrogen.

The theoretical tolerances of the other two patients for ingested oil were

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also outside the realm of practical significance. It was not surprising, therefore, that the earlier oil-ingestion experiments resulted negatively, as cited below.

With one exception, the ingestion of U.S.P. cottonseed oil in amounts up to 30 ml. caused no symptoms of any sort. The exception was encountered in Sen who was revolted by the taste of the oil and developed mild, transient nausea after ingesting 20 ml. on two occasions. She made no complaints when given a similar meal of corn oil. The nausea was interpreted as being due to slight rancidity. It was not referable to allergy in view of the patient's history that her sole clinical response to cottonseed allergens was bronchial, regardless of whether it was contacted by inhalation or by ingestion.

No effect was noted in the remainder of the group after ingesting the following volumes of U. S. P. cottonseed oil: duV, 2 ml.; Woo, 20 ml., and Sae, 30 ml. In view of the high ingestion thresholds determined for the water-soluble constituents of cottonseed and in face of the low nitrogen content of the oil, it would have been safe to have offered much larger measures of oil for these ingestion studies, and even to have tested concentrated washings in large volumes by the oral technique. It is hoped to do so in the future.

DISCUSSION

Although tests of the skin are of value for screening purposes, it has always appealed to the author that the ultimate diagnostic procedure for allergic cases should be applied to the organ involved in the clinical complaint; such as the nose or the eye of the hay fever patient, the bronchial mucosa of the asthmatic, the gastrointestinal tract of the food-sensitive individual. Tests of the skin seem especially undependable in the case of food allergy because the results so seldom parallel the clinical complaint, misleading one by false positive as well as by false negative findings. This unreliability has no doubt been responsible for the optimistic claims made for such procedures as the leukopenic index.

Although some food allergists have recently veered away from cutaneous techniques and are resorting to ingestion tests, they have failed to make adequate distinction between allergenic and psychogenic results. Furthermore, little or no attempt has been made to appraise the degree, or threshold, of sensitization by means of ingestion studies.

In the present study, the author has aimed to overcome these two shortcomings of the otherwise promising ingestion test by (1) conducting all feeding experiments in a masked manner so as to control psychic factors, and (2) by using measured amounts through the feeding of standardized extracts in increasing doses at half-hour intervals until allergic symptoms develop. These principles have been recently applied to corn allergy in the form of standardized test puddings, carrying labels which could not be decoded by the physician or his patient until the entire experiment, with

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control as well as allergenic meals, had been concluded. The results will soon be published.

By resorting to extract rather than food, we have been able to use as a test meal the same extracts as those employed for concurrent threshold tests of the skin, eye and serum-sensitized site. In time, such parallel studies should permit a statistical evaluation to be made of the various tissue tests in terms of the clinical or ingestive test. Eventually, one should be able to eliminate the more complicated ingestion procedure. By applying an ingestive index to the value determined by one of the tissue tests, one should be able to calculate what the approximate clinical tolerance would be. This diagnostic short cut could only be used, of course, with those allergens which produce reliable cutaneous and/or conjunctival reactions. Cottonseed falls in this class. For less dependable foods, the ingestion test would probably have to remain the guide to sensitivity.

The figures given in the tables of this article are based on approximate endpoints and a limited number of patients. They are the outcome of pilot experiments which aimed to determine differences in the order of magnitude between ingestive and tissue tolerances and to work out a new, more objective approach to the diagnosis of food allergy. They also describe a means of appraising roughly the clinical significance of any contaminating allergen in edible oils. It is hoped that similar studies will be instituted by others so that the clinical significance of various tissue tests may eventually be expressed as an index.

CONCLUSIONS

1. Through controlled conjunctival, intracutaneous and scratch tests, the minimal amounts of extract required for the allergic responses have been determined for four cottonseed-sensitive patients. The amounts needed for the Prausnitz-Kustner test and for exhaustion of serum reagins have also been estimated by means of passive transfer studies.
2. A new type of threshold ingestion test has been described which uses the same preparations of seed extract as those employed for concurrent tissue-tests.
3. Ratios calculated by comparing the results of the ingestion method with those found by tests of the other tissues reveal that hundreds to millions of times more nitrogen is required for the response to ingestion than for the first reaction of the skin, conjunctiva or serum.
4. Comparisons between the responses to extract and to saline washings of cottonseed oil indicated that little if any seed allergen remains in the oil. Indeed, liters of oil would have to be consumed even to approach the ingestive or clinical doses of any of our patients.
5. It is hoped that the general principles outlined for the more scientific

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COTTONSEED PROTEIN vs. COTTONSEED OIL SENSITIVITY

V. Cottonseed Asthma: Protein vs. Oil

JOHN H. MITCHELL, M.D., F.A.C.A.
Columbus, Ohio

BECAUSE sensitivity to the protein fraction of cottonseed is often of high degree, allergists have advised avoidance of dust from mattresses and furniture stuffed with cotton linters, foods containing cottonseed flour, and cottonseed oils used in salad dressing, vegetable shortening and oleomargarine. Theoretically there is no reason to anticipate that sensitivity to the water-soluble cottonseed protein would indicate associated sensitivity to the oil. However, it has been assumed that the refined oil might contain traces of protein sufficient to produce symptoms.

Most authors of books on allergy published between 1931 and 1939, by inference or by direct statement, indicate that the oil should be avoided. In 1940, Bernton, Spies, and Stevens,² in their study of five cases highly sensitive to cottonseed protein, concluded that "Patients who are sensitive to the water-soluble cottonseed extractives may safely be spared the inconvenience of attempting to avoid foods containing cottonseed oil." This research gave the writer courage to discontinue advising cottonseed protein-sensitive patients to avoid cottonseed oil products. Later, clinical tests were made using the oil in tablespoonful doses orally, followed by 1 c.c. doses intramuscularly. No local or constitutional reactions resulted, and it was assumed that the problem was solved.

However, since 1940, at least eight books on allergy have reiterated the warning that clinical symptoms could and often did follow ingestion of the oil. The most lenient attitude was expressed by Unger⁷ in 1945 when he stated, "There is some doubt as to the allergenic role of foods . . . which contain cottonseed oil; until this is cleared up, such foods should be avoided." At the other extreme, Rowe⁸ writes, "Sensitization to cottonseed allergen, especially by inhalation, may be as severe as any encountered. Such patients usually cannot take any cottonseed oil or fat by mouth without severe symptoms." In 1945, Criep,⁹ also discussing cottonseed sensitivity, stated, "There is serious doubt as to whether the ingestion of cottonseed oil may give rise to allergic symptoms, although this is probable in patients who are extremely sensitive to cottonseed. In these instances the sensitivity must be to a water-soluble fraction of cottonseed." No clear statement could be found in the literature except that of Bernton, Spies and Stevens which unequivocally removed the suspicion that ingestion of cottonseed oil would be harmful to cottonseed protein-sensitive patients.

The question of the antigenicity of vegetable oils arose again late in 1947

From the Department of Medicine, Ohio State University, Columbus, Ohio.
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TABLE I. COTTONSEED ASTHMA: PROTEIN VS. OIL

Case No.	1	2	3	4	5	6	7	8	9	10	11
Sex	M	M	M	M	M	M	M	F	F	M	F
Age of onset (in years)	3	½	2	2½	1½	1	18	16	8	31	½
Age came for treatment	6	10	5½	9	3½	13	24	18	21	33	31
Age December 31, 1948	21	24	18	21	13	21	31	22	22	34	32
Years observed	15	14	12	12	10	8	7	4	1	1	½
HISTORY OF SYMPTOMS FROM CERTAIN BRANDS OF:											
fig newtons	+	+	+*	+		+	+	+		+	
cookies	+	+		+	+	+	+	+		+	
cup cakes	+	+		+	+	+	+	+		+	
graham crackers	+				+	+		+			+*
health bread											
candy bars	+										
"cake" doughnuts	+*	+*			+	+	+		+	+	
"raised" doughnuts	o	o	o	o	o	o	o	o	o	o	o
salad oils	o	o	o	o	o	o	o	o	o	o	o
vegetable margarine	o	o	o	o	o	o	o	o	o	o	o
oleomargarine	o	o	o	o	o	o	o	o	o	o	o
Serology	o	o	o	o	4+	o	o	o	o	o	o
Passive Transfer	+	+	+	+	o	o	o	+	+	+	o
PROTEIN FRACTION											
Prick tests											
Cottonseed 1%	4+	4+	4+	6+	4+	4+	4+	2+	4+	4+	8+
CS-1A**	6+	10+	4+	10+	4+	6+	4+	3+	6+	6+	10+
Conjunctival tests											
Cottonseed 0.1%	4+	4+	2+	4+	2+	o	2+	2+	2+	2+	4+
Immunizing injections	+*	+*	+	+*	+	+	+*	+	+	+*	
TESTS WITH COTTONSEED OIL											
Skin (prick method)	o	o	o	o	o	o	o	o	o	o	o
Conjunctival	o	o	o	o	o	o	o	o	o	o	o
Nasal	o	o	o	o	o	o	o	o	o	o	o
Oral	o	o	o	o	o	o	o	o	o	o	o
Ingestion 15 c.c.	o	o	o	o	o	o	o	o	o	o	o
Inhalation	o	o	o	o	o	o	o	o	o	o	o
Injection 1.0 c.c. (I.M.)	o	o	o	o	o	o	o	o	o	o	o

Unfilled spaces indicate test was not made.

*Indicates constitutional reaction.

**CS-1A, a highly purified cottonseed protein fraction obtained from Henry Stevens, Ph. D., Head, Allergen Research Division, United States Department of Agriculture.

when hearings of the Federal Security Agency were held and leading allergists were asked to testify. The testimony of G. T. Brown and McGrath indicated that from their clinical experience many patients sensitive to cottonseed protein also developed symptoms when the oil was ingested. A contrary opinion was given by Bernton, Mitchell, Figley, and Loveless. None of these latter witnesses had observed a cottonseed protein-sensitive patient in whom it could be conclusively demonstrated that the oil was capable of producing allergic symptoms. A verbatim record of the testimony taken at these hearings has been recently published.¹ Figley,¹ in his presidential address before the American Academy of Allergy, presented the present status of the problem, summarizing the testimony given in the hearings, and gave a detailed description of the oil refining process.

The object of this communication is to present the writer's experience in this controversial area.

Of 906 nonseasonal extrinsic asthmatics, thirty-seven (4 per cent) gave positive skin reactions to cottonseed protein by the scratch or prick method.

Table I summarizes the results in a study of eleven highly sensitive cases,

COTTONSEED SENSITIVITY—MITCHELL

eight males and three females, observed from eight months to fifteen years. The age of onset of asthma was before three years in seven cases. All had experienced severe asthma following exposure to cottonseed protein by inhalation, ingestion, or injection. The history indicated that the eating of certain brands of fig newtons, cookies, cup cakes, graham crackers, health breads, "cake" doughnuts, and candy bars was followed within a few minutes by one or more of the following symptoms: tingling and edema in the mouth and tongue; nausea, vomiting, and abdominal cramps; generalized itching and urticaria; and asthma. "Raised" doughnuts and edible cottonseed oils could be eaten with impunity.

Prick tests on the upper back, with cottonseed protein (Arlington) and CS-1A,⁶ 1 per cent in glycero-saline, gave consistently positive reactions, generally larger wheals being obtained from the latter extract.

Conjunctival tests with cottonseed protein (Arlington) 0.1 per cent in saline were positive in all except Case 6. Subsequently, he experienced a sharp attack of asthma following the inhalation of a small quantity of powdered antigen.

Passive transfer tests were positive to cottonseed protein in six, negative in three, and not done in two instances.

Specific immunizing injections up to .5 c.c. of 1:1,000 dilution had been given to all but Case 11, and constitutional reactions were encountered in five.

In sharp contrast were the results of experiments with undiluted cottonseed oil (Wesson oil, purchased at a local grocery) which was instilled into the conjunctival sac, dropped into the nose, inhaled in nebulized form, ingested in 15 c.c. amounts and injected intramuscularly in doses of 1 c.c., without producing any local or constitutional reactions. Prick tests on the upper back were also negative.

These experiments indicate that edible cottonseed oil lacks the capacity to produce allergic symptoms, even by intramuscular injection, in patients known to be highly sensitive to cottonseed protein.

SUMMARY

1. Eleven asthmatics, clinically and immunologically highly sensitive to cottonseed protein, were exposed to edible cottonseed oil by skin tests, mucous membrane tests, inhalation, ingestion, and intramuscular injection without local or constitutional reactions.
2. These experiments confirm the opinion of Bernton, Spies, and Stevens and provide additional evidence that sensitivity to cottonseed protein does not indicate concomitant sensitivity to cottonseed oil.
3. In view of the above findings it seems unnecessary to advise patients sensitive to cottonseed protein to avoid foods containing cottonseed oil.

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IDIOLBLAPTIC ALLERGY AS AN IMPLEMENTING BACKGROUND FACTOR IN ANTERIOR POLIOMYELITIS

An Exploratory Study

ARTHUR P. LOCKE, Ph.D.
New Brunswick, New Jersey

and

ARTHUR F. COCA, M.D.
Pearl River, New York

THE roots of this investigation reach back to the finding by Boone, Chase, and Brink,¹ that bacteria not normally invasive from the intestine become invasive during anaphylactic shock. The ability of shock to open the doorway to invasion by latent and low-grade infection has been further investigated by Weisberger,¹² Burn, Chandler and Hartshorn,⁴ and others, and discussed by Locke⁸ and by Good and Campbell,⁷ who were able to implement the precipitation of a latent viral herpetic infection, in the rabbit, by means of induced anaphylactic shock.

The diagnostic criterion of the presence of the reaction to ingested food that has been described by Coca as *idioblapsis* is a rise in pulse rate so far exceeding that produced by the ingestion of foods which do not cause that disturbance as to suggest the production of a shock-like reaction in the areas most affected.

Coca had found an association between freedom from idioblastic allergy and freedom from common cold. In a group carefully screened for presence of the revealing, excessive pulse rise following ingestion, and free also of a series of associated symptoms (headache, et cetera) which had been found by him to occur so commonly during the reaction phase of idioblastic allergy as to have value as accessory indications, about 8 per cent were found who had no recognized signs of the presence of idioblastic allergy. Of this 8 per cent, none was subject to common cold. Conversely, in the total of fifty-two persons in the group who appeared to be cold-free, only fifteen appeared to have any allergic symptoms. The symptoms occurred, in these fifteen, rarely, or occasionally, or "at the menstrual period," or "formerly," or only from a certain food which the individual had learned

From the Sister Elizabeth Kenny Foundation, Minneapolis, Minnesota.

After this investigation had been concluded, the voluminous records analyzed and the results tabulated for publication by Doctor Locke, he suffered a severe illness which has prevented him from preparing the usual explanatory report. Doctor Locke had all the material sent to Dr. Arthur F. Coca with a request that he undertake the writing for him. Doctor Locke has read and corrected the manuscript, and fully approves its factual content.

Two circumstances greatly influenced the launching and conduct of this investigation. The first of these was the active interest of Dr. Fred W. Wittich. Dr. Wittich placed the plan before Mr. Marvin L. Kline, director of the Sister Elizabeth Kenny Foundation in Minneapolis, offering his service in furthering the work; and he was successful in obtaining the Foundation's approval and financial support of the undertaking. The second important circumstance was the enlistment, as investigator, of Donna B. Baughman. Mrs. Baughman was specially trained in the procedure, and was at home in Minneapolis where the study was made. Every courtesy and facility was given her at the Foundation, including office accommodation for the interviews. Dr. John F. Pohl was especially helpful in the arrangements for comprehensive interview and inquiry into family background, as was Dr. S. R. Seljeekog in making available the extensive files of the Sister Kenny Institute. The "control" group were students at the Southwest High School of Minneapolis, who were made available for study through the co-operation of Dr. Alice Hartig, medical director of the Minneapolis Public School System. It is a pleasure to acknowledge the interested co-operation of Dr. Samuel L. Hicks, superintendent of the Pearl River school, in the control survey for that locality reported in Tables I and III.

Doctor Coca is an Honorary Fellow of the American College of Allergists.

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to avoid. Thus the cold-free individuals were those either altogether free from idioblastic allergy or those with an allergy classifiable as mild or well controlled. Several of the group who previously had been frequently subject to common cold became cold-free following identification and elimination of food allergens from the food intake.⁵

Locke, in a study made in collaboration with Brown and associates at Stephens College, found a quantitative association between number of symptoms pointing toward presence of idioblastic allergy and number of colds developed. Students found at the beginning of the school year to have a total of zero to one indication of presence of allergy developed during the subsequent year an average of $0.94 \pm .08$ colds, as contrasted with the average of $3.41 \pm .29$ colds for the students found at the beginning of the year to have a total of more than nine indications of presence of allergy.³ A related approach was used in his analysis of the data collected in this investigation of background factors in poliomyelitis.

The idea that idioblastic allergy may predispose to poliomyelitis was suggested by a report that about 90 per cent of adults examined carry in their blood antipolio protective antibodies. These figures suggest that about 10 per cent of the population may be naturally resistant to the virus of poliomyelitis, which therefore does not gain immunologically effective entrance. This percentage is close to that which has been found for persons appearing to be naturally resistant to the common cold (near 10 per cent, according to Paul and Freese¹⁰; near 12 per cent, according to Brown²; near 12 per cent, according to Locke⁹; and near 12 per cent, according to Coca.⁶

The "low-grade" infective power of the polio virus in the sense of Locke is indicated by the fact that only a small percentage of infected persons develop a clinically recognizable case of polio,¹¹ and of these about 75 per cent recover without residual disability.

The following differences exist between the common cold and poliomyelitis as subjects for an investigation of this type:

1. It is easy to identify the cold-resistant person by mere questioning; whereas one can identify the persons that presumably are naturally resistant to poliomyelitis only through the questionable negative finding in an examination of the blood for polio-protective antibodies.
2. It is likewise easy to identify cold-susceptible persons; whereas most polio-susceptible persons that actually become infected present no characteristic symptoms of the disease at any time.
3. Infection with the cold virus is indefinitely recurrent due to the short term of the acquired immunity; and this circumstance permits the observation of any resistance to that infection which may at any time be experimentally induced.
4. On the other hand, a person's first effective exposure to the virus of poliomyelitis results in an infection, with or without noticeable symptoms.

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TABLE I.

Frequency with which hives, heartburn, etc. were reported as a recurring experience by the persons questioned in the contrasted control and polio groups.

Symptom weight (as an indication of tendency to food allergic reaction)	Percentages subject to Hives, Heartburn, etc.					
	Control Group			Polio Group		
	Male	Female	Combined	Male	Female	Combined
(1) Hives	16	20	18	13	27	19
(0) Heartburn	19	10	15	14	13	14
(1) Canker Sores	60	64	62	54	63	58
(1) Constipation	4	9	6	20	35	27
(1) Rhinitis	17	21	19	27	29	28
(1) Nervousness	6	11	8	8	21	13
(0) Stammering	10	4	7	9	6	8
(0) Enuresis	7	7	7	28	16	23
(0) Asthma	10	4	7	1	7	4
(1) Headaches	29	23	26	43	34	38
(1) Indigestion	30	30	30	32	41	36
(1) Tiredness	5	12	8	15	21	18
(1) Dizziness	29	23	26	14	25	19
(0) Hemorrhoids	0	0	0	4	6	4
(1) Neuralgia	15	21	18	33	33	33
(0) Hay Fever	25	14	19	5	9	7
(0) More than two colds per year	47	43	45	58	56	57
(0) % with not more than 1 cold per year and no rhinitis			17			9
(2) Pulse above 84	11	16	13	30	33	31
Total Number	126	120	246	142	107	249
	Control Parent Group (137)			Polio Parent Group (399)		
(1) Parent with a total symptom weight of 2 or more*	64			90		
Percentages of the control and polio groups with a total symptom weight of 2 or more* Pearl River Students	71 67			100		

*Maximum pulse above 88 in pulse range test, or pulse range exceeding 14, also given a weight of 2 in the absence of pulse above 84—for the computation of total weight only.

which is regularly followed by the production of a lasting immunity. Hence any attempt to establish a resistance to the virus of poliomyelitis must be made in advance of the individual's first exposure, and the efficacy of the procedure has to be evaluated through statistical analysis.

Notwithstanding these several relative handicaps, and the further limitation that no "control" group was available that consisted of more than a small fraction of actually polio-resistant persons,* the investigation was begun on August 1, 1948, and continued to February 1, 1949.

Two groups of individuals were examined for the symptoms and signs of idioblastic allergy that are listed in Table I. One group consisted altogether of known victims of poliomyelitis; and the other ("control" group) consisted entirely of boys and girls, of age thirteen to nineteen, with no characteristic symptoms of infantile paralysis at any time in their lives and with no close relative who had ever developed infantile paralysis.

The procedure was modified from that used by Locke in the Stephens College study in the addition to the list of conditions on which information

*A large part of the population is not resistant to polio but immune to it as a result of a presumptive immunizing but nonparalytic attack. The naturally resistant individual differs from the immune individual in that his protection derives from an absence of factors predisposing to infection rather than to a presence of immune antibodies produced following an earlier attack.

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TABLE II. PERCENTAGES FOR THE POLIO SERIES EXAMINED WITH RESPECT TO AGE GROUPINGS

Age	3-7	8-12	13-19	20-45	Combined
Total number	68	80	69	32	219
Hives	16	14	22	31	19
Heartburn	9	6	16	50	14
Canker sores	22	65	58	72	58
Constipation	25	26	17	41	27
Rhinitis	15	29	32	41	28
Neuroleptic	9	13	12	28	13
Stammering	7	10	7	3	8
Enuresis	25	25	17	22	23
Asthma	4	1	6	3	4
Headaches	26	36	32	56	38
Indigestion	26	43	32	50	36
Tiredness	13	15	20	31	18
Dizziness	1	19	22	50	19
Hemorrhoids	0	1	1	25	4
Neuritis	21	36	35	41	33
Hay fever	1	4	11	9	7
Pulse above 84	36	30	25	36	31
More than two colds per year	69	56	48	53	57

was sought, of several conditions which had since been observed as accompaniments of idiopathic allergy. These were enuresis (proved allergic in one case by its complete absence for one and one-half months during avoidance of the few pulse-accelerating foods and its prompt recurrence when these foods were returned to the diet), stammering,* and hemorrhoids (similarly proved allergic). Among these three, only the data concerning enuresis provided a significant percentile difference in its occurrence in the polio and the control groups.

Mrs. Baughman questioned her subjects and their parents carefully, and the symptoms recorded were those appearing to recur in cause and effect relationship with a food source and, in the polio series, *previous* to the poliomyelitis attack.

Blood pressures were noted in some of the parents without any useful differentiating conclusions being derived from those data.

The occurrence of hay fever and bronchial asthma was noted, although the former purely reaginic, atopic manifestation does not come into consideration in the present problem. The lower incidence of hay fever among the polio group is due to the relatively younger ages of most of the individuals in that group as compared with the high school student controls.

Incidentally this difference in the ages of the two groups makes the markedly higher incidence of some allergic symptoms among the younger polio group the more significant of their predisposing influence, since the incidence of all those symptoms, excepting enuresis, tends to increase with age. It seems of possible special interest, pending confirmation, that the incidence of neuralgia among the polio group was even higher among the polio group of ages eight to nineteen (35.5 per cent) than it has been found by me in fifty-four allergic adults (27.8 per cent).

A general summary of the quantitative findings of this investigation, as collected and classified by Locke, is presented in Table I.

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TABLE III.

Showing marked difference in the incidence of seven allergic manifestations among the polio cases and the controls.

Symptom	Polio cases (249) per cent	Controls	
		Minneapolis (246) per cent	Pearl River (269) per cent
Enuresis	23	7	7
Constipation	27	6	12
Abnormal tiredness	18	8	9
Pulse over 84	31	13	—
Rhinitis	28	19	14
Neuralgia	33	18	15
Headaches	38	26	20

In Table II the data from the "polio group" are reclassified according to the ages of the individuals.

In Table I it is seen that the incidence of some symptoms, for example, hives, heartburn and canker sores, is approximately the same in both groups. However, the incidence of other symptoms is markedly different in the two groups, and it is *always greater* in the polio group. The symptoms whose incidence differed widely in the two groups are listed in Table III. Included in the table are the corresponding figures obtained in a similar survey which I carried out in the winter 1948-9 among the high school students in Pearl River, who constitute a convenient second control group.

Another marked quantitative difference in the polio and control groups seems significant. In Minneapolis, it was found that *all* victims of polio presented two or more symptoms by "weight"† of food allergy whereas 29 per cent of the control group showed either no allergic symptoms or only one symptom. Among the students in the Pearl River High School 33 per cent reported fewer than two symptoms—confirming Locke's result. This difference was found in Minneapolis to extend into the families. Ninety per cent of the polio-parent group had more than two symptoms against only 64 per cent for the control-parent group.

DISCUSSION

These consistently wide differences, especially when they are considered in the light of the comparable studies of the relationship of idioblastic allergy to susceptibility to common cold, suggest that children born free from idioblastic allergy or rendered free from its hazard through identification and avoidance of all pulse-accelerating allergens⁶ may be either quite resistant to the virus of poliomyelitis or at least safe from the serious consequences of that infection.

The results of this study suggest four categories of the population with

†The "weight" of indication of the presence of idioblastic allergy increases with the number of symptoms reported which are known to be commonly associated with that condition. Pulse above 84 and/or a maximal pulse above 88 in a pulse-range test, or pulse range exceeding 14, were given a weight of 2 since these indications have been found to point unquestionably toward presence of idioblastic allergy.⁶ Weights of 1 were assigned to the findings in Table I which have been found to be suggestive of the presence of idioblastic allergy but not conclusive in the absence of corroboration by the objective pulse-range test.

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respect to idioblastic allergy and infantile paralysis: (1) those free from reaction to an idioblastic allergy and therefore quite resistant to the virus, (2) those few who are markedly affected by a certain type of idioblapsis (defined for the present by the seven manifestations listed in Table III), and therefore in special danger of the serious consequences of the infection, (3) those less markedly affected by the allergic handicap and therefore able to cope with the infection without suffering recognizable damage, and (4) those immune as a result of earlier, nonparalytic exposure.

The findings also suggest study of certain appropriate therapeutic measures.

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A CLINICAL EVALUATION OF CHLORCYCLIZINE (PERAZIL)

ETHAN ALLAN BROWN, M.D., F.A.C.A., Boston, Massachusetts
LOUVANE A. FOX, M.D., Keene, New Hampshire
JOSEPH P. MAHER, M.D., F.A.C.A., Boston, Massachusetts
CONRAD NOBILI, M.D., F.A.C.A., Quincy, Massachusetts
RUSSELL C. NORTON, M.D., Manchester, New Hampshire
THEODORE SANSELLA, M.D., Revere, Massachusetts

AN EXAMINATION of the literature on antihistaminic agents demonstrates the fact that there is, as yet, no satisfactory objective method for their clinical evaluation. The usual routine followed consists of the selection of a group of allergic patients (no two of whom are alike) to whom the drug is administered under very varied circumstances. The patient's opinion is the only actual criterion available. When lesions (such as hives) are visible, there can, of course, be no doubt as to their disappearance. When a nose is, however, considered less stenotic, or pruritus less severe, the criteria are less acceptable.

The following paper makes no new contributions as to method of study, except to list the patients as to the dosage level at which they were relieved. Their comments regarding the efficacy of the drugs they used are accepted in full. Relief is defined as complete or almost complete freedom from symptoms. Any other report is taken as subjective and listed as meaning that the ingestion of the drug was without effect. The patients presented the usual allergic syndromes observed during the tree, grass and ragweed pollen seasons of 1949 in New England. The effects of Perazil upon several miscellaneous conditions are also listed.

One observation of interest may be made at this point. The opinions of the six physicians who did the study were by no means unanimous, and the evaluation therefore concerns them as individuals, in that some (EAB and RCN) consistently achieved better results than did the others. One reported the poorest results (JPM), and the other three were consistent in the number of patients relieved and the degree of relief or side reactions. Had all six of us written individual papers, the results would have been as varied as those noted in the literature for other drugs of the same type. It would seem, therefore, that the percentile reports by individual physicians who study small groups of patients are limited in applicability and that the results achieved by a number of physicians working together with large groups of patients would result in internal checks and balances within the group and therefore reflect, perhaps, data more nearly authentic. This, again, can only be acceptable against the background of the type of patients seen, as in private practice, public clinics, or compensation clinics, the type of sensitivity and the severity of the symptoms, the season, the specific

Allergy Section, Boston Dispensary Unit, New England Medical Center, Boston.
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Drs. Fox, Norton, and Sannella are associate members of the American College of Allergists.

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treatment given, and the general geographical location of the clinical evaluation experiment.

ANIMAL PHARMACOLOGY

Since Chlorcyclizine is a new drug, its bibliography is limited. The compound has the structural formulae N-methyl-N'-(4-Chlorobenzhydryl) piperazine. The pharmacological action in animals has been reported on by Castillo and his colleagues,¹ whose studies show that Perazil had four times greater potency than Benadryl, as tested by its effect on the histamine-induced contractions of the isolated guinea pig tracheal chain. Perazil acts more slowly than Benadryl, and its antihistaminic effect lasts longer after washing. One hour after an oral dose of 2.5 mg./kg. of Perazil, 62 per cent of thirty-seven guinea pigs are protected from nebulized 0.2 per cent histamine diphosphate, while at four- and five-hour periods, 83 per cent and 69 per cent are, respectively, protected. From a comparative point of view, Tagathen protects 63 per cent, one, four or five hours after dosing; Neo-Antergan protects 60 per cent, 40 per cent and 60 per cent, respectively, while Pyribenzamine and Thenylene are markedly less effective.

The oral administration of Perazil in doses of 10 mg./kg. prevents or reduces the severity of broncho-constriction following exposure of guinea pigs to nebulized histamine, up to twenty-three hours. An intravenous injection of 3 mg./kg. into anesthetized dogs blocks almost completely the depressor effect produced by 50 micrograms of histamine diphosphate for a period of up to two hours. The spasm produced by histamine on the isolated guinea pigs ileum is antagonized by Perazil as are the spasmogenic effects of acetylcholine and barium chloride.

When Perazil is given intravenously to dogs in doses of 3 mg./kg., the blood pressure falls 33 to 90 mm. of Hg., but in all instances returns to normal within three minutes.

The local anesthetic activity of Perazil in guinea pigs is the same as that of Benadryl when tested by the intradermal wheal method, a 1 per cent solution of each drug producing anesthesia lasting twenty-two minutes. A test of the mydriatic action on the rabbit eye shows a 1 per cent solution of Perazil as negative, while a 1 per cent solution of Benadryl produces a 20 per cent dilatation of the pupil.

The LD₅₀ of Perazil in mice is 137 mg./kg., as compared to Neo-Antergan (115), Tagathen (105), Thenylene (77), Pyribenzamine (67), and Benadryl (69), respectively.

HUMAN PHARMACOLOGY

The human pharmacology was studied by Jaros and his colleagues.² In thirty subjects, of whom sixteen were allergic and fourteen non-allergic, fifteen were treated with 100 mg. of Pyribenzamine and fifteen with 100 mg. of Perazil. Scratch tests were performed with 1:4,000,000 to 1:512,000 histamine solutions. The patients were then reversed, those receiving

Pyribenzamine being given Perazil and vice versa. Perazil produced a greater degree of inhibition of the wheal response than did Pyribenzamine, the effects lasting about thirty-two hours longer. In one test with the 1:256,000 dilution of histamine four hours after a dose of Pyribenzamine, fourteen of fifteen patients had wheals 1 to 2 mm. in diameter, while only two of fifteen treated with Perazil had similar wheals. In a cross-over experiment, four of fifteen treated with Perazil had wheals 0.5 to 2 mm. in diameter, while thirteen of fifteen given Pyribenzamine presented wheals 0.5 to 2 mm. in diameter. Of a total of sixty-three doses of Perazil, seventeen caused drowsiness, while twenty-four of fifty-six doses of Pyribenzamine had the same reaction. The degree of drowsiness, however, was milder after Perazil than Pyribenzamine. Side reactions, which included dryness of the mouth, nausea, headache, light-headedness, nervousness and similar reactions, occurred in only twenty-one of the sixty-three patients given Perazil, and in thirty-three of the fifty-six patients given Pyribenzamine.

CLINICAL REPORT

In a later communication, Jaros³ reported on twenty-three patients with hay fever, eight with atopic dermatitis, twenty-one with vasomotor rhinitis and six with acute urticaria. Only one patient with hay fever and three with vasomotor coryza failed to obtain excellent relief. Moderate improvement was obtained in eight of twelve patients with bronchial asthma. Of the eighty-four patients treated, those receiving hyposensitization and Perazil had the greatest degree of relief, with only four patients presenting mild side effects, the most frequently being drowsiness. All of the patients had had moderate to severe uncontrolled symptoms, despite the use of other antihistaminic agents.

HAY FEVER

In the present study there were, in all, seventy-five patients with "pure" hay fever. They are listed according to their dosage level. Seven required only one-half tablet, that is 25 mg., on arising to achieve complete control of their symptoms which were only present in the morning. Some of these patients required an additional 25 mg. when necessary. In none were there any side reactions, and in all, the good effect lasted the full twenty-four hours, excepting for occasional symptoms following exposure to pollen.

Two patients with uncomplicated hay fever required either 25 or 50 mg. for complete relief of their symptoms. In one of these there was moderate drowsiness. This same patient suffered from severe drowsiness with fair relief from Pyribenzamine. He could, however, take Trimeton with no drowsiness and equally good effect.

Three patients with hay fever discovered that they achieved excellent results when they took 25 mg. twice daily, making a total intake of 50 mg.

One of these complained of slight, questionable light-headedness. Neither of the other two presented side reactions. One of these patients achieved equally good results with Pyribenzamine and Trimeton, although he stated that the effect of Perazil was longer than that of any of the other anti-histaminic agents he had taken. One additional patient required 25 mg. three times daily, with complete relief and no side reactions.

There were eighteen patients who took a single tablet of 50 mg. when necessary for complete relief in all and no side reactions. One of these patients had little relief with Decapryl, better with Trimeton, and excellent with Perazil. Another reported moderate relief with Pyribenzamine and excellent with Perazil, and a third achieved good relief with Trimeton but better with Perazil. One reported wakefulness from Trimeton, although the therapeutic effects were excellent. Perazil gave an equal degree of relief with no wakefulness.

Thirty-six patients of this group suffering from hay fever took 50 mg. twice daily. Fourteen of these had never had any other antihistaminic drug. They achieved complete relief with no side reactions. One of these reported moderate relief with Pyribenzamine, which, however, caused drowsiness. Another patient had extreme drowsiness with both Pyribenzamine and Benadryl, with no side reactions from Perazil. Two others, who had had complete relief with Perazil, with no side reactions, achieved equally good relief with Pyribenzamine and Benadryl, which, however, did not last as long. Two patients who reported complete relief with Perazil had such drowsiness with Benadryl that they could not continue their work. They also achieved moderate benefit with moderate drowsiness from Pyribenzamine. One patient had equally good results from Perazil and Trimeton, with no side reactions from either. This same patient was not benefited from Pyribenzamine and had drowsiness with Benadryl. One patient found Trimeton and Perazil of equal value. This same patient had complete relief with no drowsiness with 25 mg. doses of Benadryl, and complete relief and moderate drowsiness with 50 mg. of the same drug.

In the comparative studies done with patients with hay fever who took 50 mg. of Perazil twice daily, one, who achieved complete relief in forty-eight hours, stated that Perazil lasted longer although it gave equally good relief as compared to Pyribenzamine. Another patient discovered that he had required four doses of other antihistaminic agents, including Benadryl and Pyribenzamine, but only two doses in twenty-four hours when he took Perazil. He suffered from no side reactions. One patient stated that Pyribenzamine and Perazil worked equally well, except that the former caused slight drowsiness, the latter causing no side reactions. One patient, who had excellent relief with Trimeton, said that he had equally good but longer-lasting effects with Perazil. One patient, with no relief from Pyribenzamine and fair relief at night with drowsiness from Trimeton, had complete cessation of symptoms and no side reactions with Perazil. Two other patients found Trimeton and Perazil equally good with no side re-

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actions and complete cessation of symptoms. One patient, who achieved complete relief with no side reactions from Trimeton and Perazil, stated, however, that he preferred Trimeton.

The side reactions require some note. There were, in all, five patients in whom they occurred. In one, they were of moderate degree and consisted of drowsiness, shakiness and palpitations, although relief of allergic symptoms was complete. One patient, who had extreme drowsiness with Pyribenzamine, had slight drowsiness with Perazil. One patient with moderate drowsiness, nausea and light-headedness preferred Pyribenzamine. Repeat doses of Perazil brought on the same side reactions. One individual who had slight nausea for the first three hours after he took Perazil was thereafter able to take it without ill effect. This same patient received no benefit from Pyribenzamine. One patient had slight drowsiness with 50 mg. twice daily but could tell no difference between Pyribenzamine and Perazil, both working fairly well for moderate symptoms but neither having any effect when the hay fever was severe.

Some patients with hay fever required larger doses. One with a great sensitivity to ragweed required 50 mg. of Perazil three times daily with no ill effects and with excellent relief, and one patient required 200 mg., that is, four doses in every twenty-four hours, to achieve complete relief, the side reactions being slight drowsiness. One patient, who took one tablet on arising and retiring with complete relief, with an additional 50 mg. before exposure, had severe drowsiness with 150 mg. dosage level in twenty-four hours but no drowsiness when he reduced the dose to 100 mg.

VASOMOTOR CORYZA

There were, in all, seven patients who suffered from severe, typical vasomotor coryza associated with pale, boggy membranes in the absence of any signs of infection or allergy. Of these, one was completely relieved by 25 mg. taken when necessary and one by 50 mg. for occasional symptoms. One patient required 50 mg. twice daily, on arising and retiring, and a third required 50 mg. three times daily, with complete relief, none showing side reactions. The third patient, however, used nasal Antistine for occasional severe attacks. One patient in this group took 25 mg. when necessary, with improvement, excepting for side reactions of slight drowsiness, dryness of the mouth, light-headedness, and difficulty in walking. This patient claimed, however, that greater side reactions followed the use of Perazil than the use of Pyribenzamine, Trimeton, Benadryl and Ephedrine, although all gave equally good results. One patient, whose nose had never previously cleared with any medication, antihistaminic or otherwise, achieved complete relief with 50 mg. twice daily, and after two months, improved to the extent that she required only 50 mg. once daily. For a severe attack, however, the patient took three 50 mg. tablets in two hours, with complete relief and no side reactions. The last patient in this group achieved good

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results with Perazil but required Antistine nasal solution as an auxiliary medication, there being, however, no side reactions.

URTICARIA

In all, there were fifteen patients with urticaria. Of these, one required 25 mg. twice daily for complete remission of her hives, as well as for her daily headaches. This same patient had had the unusual side reaction of swelling of the ankles following small doses of Benadryl, and stomach-ache following Histadyl. Seven patients required 100 mg. daily in two doses, with complete relief and no side reactions, although one of these patients had had Pyribenzamine, Trimeton, Benadryl, Vitamin K and calcium lactate with no effect, while another had had Benadryl, Pyribenzamine, with little relief and drowsiness from these and other medications. One patient had used Pyribenzamine and Trimeton with no marked, but perhaps slight, relief, with Perazil giving complete relief for twelve to twenty-four hours. Two patients required 50 mg. three times daily, with complete relief and no side reactions. Of these, one achieved some relief with Pyribenzamine and Chlor-Trimeton, for periods up to five hours, Pyribenzamine causing slight drowsiness. In this same patient, Perazil gave relief lasting up to twelve hours. Another patient in this group had had Dramamine, which caused dizziness with the hives being worse, and Histadyl with no effect. Perazil completely controlled both conditions.

One patient took 50 mg. four times daily, with complete relief and no side reactions. This same patient had responded to Pyribenzamine, Trimeton, Chlor-Trimeton and Benadryl with slight benefit and mild drowsiness.

In this same group of patients with urticaria, there was one whose hives were associated with serum disease. He required Perazil in the 50 mg. dose every four hours, for six doses daily, with complete relief. There were no side reactions. One patient in this group took 50 mg. three to six times daily with improvement of her urticaria, but nevertheless complained of drowsiness, dryness of the mouth, nausea, light-headedness, and shakiness. She found relief with Trimeton taken during the day and Benadryl at bedtime until it was discovered that she was sensitive to chocolate, following the elimination of which she was completely well.

BRONCHIAL ASTHMA ASSOCIATED WITH INFECTION

Although antihistaminic agents have been of little use in infectious bronchial asthma or in severe allergic atopic bronchial asthma, except perhaps given intravenously, the drug was used in a group of typical intrinsic emphysematous patients, many of them suffering from nasal and sinus infection, as well as subacute bronchial infection. One of these seven was a child of six, who wheezed only with colds and was able to take 25 mg. with excellent results. One patient, whose asthma was extremely severe, was relieved of her wheezing while sitting still following a dose of 50 mg.

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She otherwise continued to wheeze moderately, although inactive. There were no side reactions in either of the patients. A third patient took 50 mg. twice daily, with mild side reactions and no relief. She claimed some relief with Perazil but insisted on the frequent use of nebulized epinephrine (1:100) and therefore cannot be used for classification purposes. Two patients took 50 mg. five times daily with no side reactions and no effects. One patient was improved on 50 mg. three times daily, claiming as good results as with Luasmin capsules, but not as good as with epinephrine (1:100) by nebulizer. The last patient in this group took 200 mg. daily, with some relief of his nasal stenosis but no effect on his cough or wheeze.

ATOPIC ECZEMA

Of the eight patients with atopic eczema, one achieved complete relief of pruritus with 25 mg. twice daily. Another required 25 mg. three times daily, with Trimeton ointment used locally. A third patient required 50 mg. twice daily, and another, 50 mg. three times daily, none of these patients presenting any side reactions. One patient used 50 to 100 mg. twice daily with no side reactions and complete relief of pruritus. Three others required 50 mg. twice daily. One of these patients also used tablets of calcium lactate, 15 gr. by mouth three times daily, and Trimeton ointment. One, although complaining of no side reactions, preferred Trimeton.

The effect of any antihistaminic is difficult to evaluate in the group of patients suffering from atopic eczema, because of the fact that almost all of them demand, if they do not require, topical applications. In all cases, therefore, the good effect must be ascribed to both methods of treatment.

In two patients in this group, who suffered both from a residual, chronic atopic eczema and a hay fever, the eczema causing little difficulty, 50 mg. of Perazil controlled both the pruritus of the lichenified areas, and the allergic coryza to perfection. There were no side reactions on 50 mg. taken when necessary.

VERNAL CONJUNCTIVITIS

The drug was used on two patients with vernal conjunctivitis; one who had received no previous relief with Benadryl and only slight help from Pyribenzamine, but marked relief from epinephrine drops lasting two hours, achieved twelve hours of relief with 50 mg. Perazil given twice daily. A second took 25 mg. twice daily, with marked relief of the ocular pruritus but little or no effect upon the conjunctival injection. Neither patient showed any side reactions.

MISCELLANEOUS CONDITIONS

Among the miscellaneous conditions treated were dermatitis herpetiformis, psoriasis, and generalized pruritus. The first patient took 50 mg. three times daily, with no side reactions and complete relief while on the medication. One patient with psoriasis, who had taken a sulfonamide and

responded with a dermatitis medicamentosa which covered the entire body, found that Perazil gave him four to six hours' relief during waking hours. Additional medication in the form of Ipral aspirin was required for sleep at bedtime. A second patient, who complained of pruritus with psoriasis, was also relieved for a period of two weeks while using local therapy which did not affect the psoriatic lesion.

An eighty-year-old woman suffering from a generalized pruritus of the senile type achieved no relief with Perazil, having taken all other anti-histaminics with no effect. One more patient with bronchial asthma and urticaria, the former being continuous and the latter occasional, had complete relief of both with 50 mg. taken twice daily, there being no side reactions.

CONTACT DERMATITIS

In contact dermatitis, we had a syndrome in which it was easy to observe the results. In all, there were fourteen patients. Of these, five took 50 mg. twice daily, and one 50 mg. three times daily, and one 50 mg. four times daily, with no side reactions and complete relief. These patients required no topical applications, excepting for the last, who used Lassar's paste. Of the remaining patients, two took 50 mg. twice daily with complete relief of symptoms and no side reactions, using Pyribenzamine cream locally. Another took 50 mg. three times daily, with little relief, the patient claiming that Trimeton and Benadryl helped to a much greater extent, there being no side reactions to any of the three drugs. One other patient took 50 mg. twice daily, using Lassar's paste locally, which did not affect the pruritus when used alone. Two patients took 50 mg. daily, using Trimeton ointment locally, and one took 50 mg. twice daily with only partial control of the pruritus, achieving better results with Trimeton tablets and ointment.

BRONCHIAL ASTHMA DUE TO FOODS AND INHALANTS

Because of the great diversity of opinion regarding the use of antihistaminic agents in bronchial asthma, the following eighteen patients, all of whom presented typical allergic chest conditions, are reported upon in detail. The dosages given vary from 12.5 mg. to 200 mg. daily.

To take them in turn, one patient, aged ten, took 12.5 to 25 mg. when necessary for complete relief of mild symptoms, 50 mg. being necessary for severe wheezing, the effect lasting twelve hours. The patient required epinephrine (1:1000) subcutaneously in addition for extreme bronchospasm.

The second patient began with 50 mg. twice daily and now achieves complete relief with one 50 mg. tablet on arising. There were no side reactions. A third patient, aged eight, took 50 mg. twice daily with complete control of symptoms and no side reactions, and a fourth compared Perazil with epinephrine (by inhalation) and ephedrine-aminophylline (by mouth) and found that the Perazil gave the most complete relief, the effect lasting

four hours, although the patient could get equal relief with Amodrine tablets or Luasmin capsules, six of either being the daily requirement. Supplementary medication consisted of potassium iodide taken throughout the course of the study for all the medications listed.

One of the patients, aged sixty-two, emotionally unstable and sensitive to dust, tobacco smoke, and cooking fumes, found the taste of Perazil repellent, although she claimed that the tablets gave her greater relief than epinephrine by aerosol, aminophylline or ephedrine (gr. 3/8). She suffered, however, from side reactions on 50 mg. taken when necessary, which she stated reduced her attacks from an average duration of three hours to one hour, with freedom until the next attack occurred. She complained of light-headedness, nervousness, shakiness, and palpitations. Similar symptoms occurred with the use of ephedrine, aminophylline and epinephrine.

A number of patients achieved complete relief on 50 mg. taken at bedtime or on arising and retiring, although one of these, aged thirty-five and sensitive to dust and grass pollens, with exacerbation with exposure to range oil fumes, had only "slight improvement" with 50 mg. twice daily.

Some of the patients were unable to give fair pictures of the results, as for instance one, who on 50 mg. twice daily had no relief whatsoever, perhaps because of her clinically proven allergic condition which was associated with a moderate emphysema and bronchitis. An emotional factor may have intervened, in that the patient's husband was hospitalized during the time she was studied. She claimed, however, relief with Trimeton, Luasmin and Hydryllin, with no relief from Perazil, which she stated caused drowsiness, nausea, dizziness, and difficulty in walking.

One of the patients who presented a typical "cold" claimed relief for both it and her wheezing with 50 mg. twice daily, which almost completely controlled her symptoms, except for an occasional slight dyspnea, and another with a plantain, mould, ragweed and house dust sensitivity showed complete relief and no side reactions during the peak of the season. Another patient studied at the same time, who, in addition to her known sensitivities to Pyrethrum and house dust, presented a severe emphysema achieved "considerable relief" with two tablets daily and better relief on 150 mg. daily, but for very severe attacks took a Luasmin capsule at the same time.

The difficulties dependent upon accurate clinical evaluation are shown by a patient, aged sixty-three, who presented known dust, ragweed and food sensitivities, with moderate emphysema, who had exacerbations due to fatigue, barometric changes and exposure to fumes. The patient, a physician, had fair results with Benadryl and Hydryllin and claimed excellent results with Trimeton and Luasmin but no relief whatsoever with Perazil, although in doses of 200 mg. daily there were no side effects. Another typical patient, aged fifty-two, with perennial wheezing associated with seasonal exacerbations due to clinically proven grass and ragweed sensitivities and house dust, but suffering as well from a purulent sinusitis and moderate emphy-

sema as well as bronchitis, had no relief from 50 mg. four times daily. There were, however, no side reactions at this dosage level.

HAY FEVER AND BRONCHIAL ASTHMA

In all, there were thirty patients who suffered both from hay fever and bronchial asthma. Their reactions fell into no apparent pattern and the results were incapable of tabulation. They are, therefore, given brief individual description. Only three demonstrated side effects; one who took 50 mg. daily in two 25 mg. doses, with an occasional additional 25 mg. for symptoms following exposure, the ill effects being drowsiness and oral dryness. This patient had similar side reactions with Benadryl, Hydryllin and Trimeton. He was, however, free of symptoms on Perazil. The second patient complained of light-headedness and headache on doses of 50 mg. when necessary, which gave him partial relief of symptoms for two to three hours equal to the relief given by Trimeton, which caused the same type of untoward effect. The third patient, who took 50 mg. when necessary, complained of extreme drowsiness and palpitations with tachycardia, sufficient to warrant cessation of treatment.

Of the other patients, one who had suffered from hay fever and bronchial asthma of fourteen years' duration, seasonal and perennial in nature with sensitivities to grass, trees and ragweed pollen and house dust, was markedly improved being free of nasal and chest symptoms on 25 mg. taken when necessary. She preferred Perazil to Trimeton, Pyribenzamine and Luasmin capsules. A patient similar in clinical pattern, a boy aged ten, with grass and ragweed pollen, mould and house dust sensitivities, had excellent relief of his hay fever and wheezing on 25 mg. when necessary, and a third patient, aged four, took 12.5 mg. twice daily for complete relief of his hay fever and wheezing for three to six hours. A fourth patient, also aged four, was completely relieved of hay fever and wheezing for twelve to twenty-four hours on 25 to 50 mg. daily.

A patient, aged eight, sensitive to cat and horse dander, grass pollens and house dust was relieved on 25 mg. twice daily, with complete relief of both nasal and chest conditions, and another patient, who took 50 mg. daily and 50 mg. when necessary, was listed among those above as having drowsiness and dryness of the mouth, although the reactions were milder with Perazil than with the other antihistaminics. One patient on 25 mg. twice daily, and another on 50 mg. when necessary, had relief lasting up to twelve hours for both conditions.

The varying patterns are demonstrated by a patient on 25 mg. twice daily, who was able to do his farming on this dose, although sensitive to dust, cattle dander, feathers, mohair and horse dander. He stated that his nasal condition was better than it had been for the last ten years despite specific and symptomatic treatment. Of the other patients on the 50 mg. dosage level, moderate severe attacks were completely relieved, but very severe wheezing required Luasmin capsules or aminophylline suppositories.

One of these was sensitive to all of the animal danders, with which he was tested, to house dust, tree, grass, plantain and ragweed pollens and to moulds.

Of the patients who took larger doses, 75 to 100 mg. daily, one was able to eat foods which otherwise caused clinical symptoms, although for severe attacks she required ephedrine in small doses.

Not all the patients behaved equally. One who took 100 mg. daily had complete relief of her hay fever but only moderate relief of her wheezing, although another on the same dosage and with tree, grass, ragweed pollen sensitivities, with additional skin tests to Alternaria and house dust, found 100 mg. daily to give complete relief with no side reactions. Another patient in this same group, however, was not as completely relieved of the asthma, although her hay fever reacted well. She could not take Trimeton because it caused drowsiness and blurring of vision.

Of five patients on the 100 mg. dosage daily, one stated that Pyribenzamine gave quicker and more complete relief and refused to continue with Perazil, although there were no side reactions. The others reported complete freedom of symptoms. One patient with hay fever and bronchial asthma, sensitive to horse dander, house dust and grass and ragweed pollens, achieved no relief whatsoever on 200 mg. daily of Perazil but was completely relieved by 50 mg. of Trimeton, there being no side reactions with either. The last patient of the series, suffering from hay fever, bronchial asthma and urticaria had complete relief of her nose and skin symptoms for twelve hours following a 50 mg. dosage, the asthma being only partially relieved and requiring epinephrine aerosol therapy every two to three hours. The same patient had previously had little or slight benefit from Pyribenzamine and Benadryl in 50 mg. doses, both causing drowsiness. There were no side reactions with Perazil.

MIXED SYNDROMES

One patient, who had hay fever and poison ivy, reported that Perazil and Trimeton both relieved the pruritus as well as the nasal condition. A patient suffering from nasal poliosis and atopic eczema responded better for her nasal symptoms than for the skin. A third suffered from hay fever and a chronic cough, with relief of the nasal symptoms, the throat condition being unaffected.

There were three patients who presented the complete syndrome of atopic eczema, hay fever and bronchial asthma. A young boy of twelve, who presented a picture of hay fever, bronchial asthma and atopic eczema, found that Perazil relieved his nasal symptoms completely on 25 mg. twice daily. His eczema was only slightly improved and his asthma unaffected. Another patient, aged eight, presenting the same syndrome, was free of nasal symptoms. He was so little relieved of his pruritus that Pyribenzamine ointment was prescribed with excellent results. A third patient found

that Perazil controlled the nasal symptoms, although he needed Trimeton ointment for his skin.

A fifty-nine-year-old patient suffering from a nasal coryza and severe nocturnal cough found his nose completely clear and his cough somewhat improved, as measured by longer periods of sleep during the night. Mercodinone (Merrell) completely controlled the cough.

SUMMARY

In all, 186 patients were treated with Perazil in doses of 12.5 to 200 mg. daily. The conditions studied were as follows: hay fever, seventy-five patients; vasomotor coryza, seven; urticaria, fifteen; intrinsic bronchial asthma, seven; atopic eczema, eight; vernal conjunctivitis, two; dermatitis herpetiformis, one; psoriasis, two; generalized pruritus, one; contact dermatitis, fourteen; atopic bronchial asthma, eighteen; hay fever and bronchial asthma, thirty; hay fever and poison ivy, one; atopic eczema and hay fever, one; atopic eczema, hay fever and bronchial asthma, three; and hay fever and allergic tracheitis, one.

Reactions were mild in one patient (not classified) and moderate, as evidenced by dry mouth, drowsiness and light-headedness, in five of the seventy-five patients with hay fever, one of thirteen with urticaria, three of thirty with hay fever and bronchial asthma, and one of eighteen with bronchial asthma. Reactions were usually associated with the doses in excess of 100 mg. daily. Although the results do not lend themselves to exact tabulations, they would appear to demonstrate Perazil—the most effective of all the antihistaminic agents so far studied by the physicians who used it.

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75 Bay State Road (Dr. Brown)

MULTIPLE SCLEROSIS AND ALLERGY MANAGEMENT WITH HISTAMINE THERAPY

Part II

HINTON D. JONEZ, M.D., F.A.C.A.
Tacoma, Washington

ALLERGY as a term was suggested by Von Pirquet⁴⁷ in 1906. Since then, it has slowly become evident that the brain and meninges, the spinal roots and the peripheral nerves may be the sites of more or less severe allergic reactions.³⁸ Kennedy,^{27,28} in 1936, directed attention to allergy as a possible basis in the production of multiple sclerosis. He stated: "Its episodes, its intermissions, the curability of its most acute crisis, its attack on the optic nerves, its neglect of sensory paths—all these things greatly resemble the happenings of localized allergic edemas after the central nervous system has come under fire. Further, the recent plaques in the rare autopsies of acute cases are not sclerotic; they are infiltrations by fluid of the nerve tissue surrounding blood vessels."

The same year Putnam³⁴ pointed to the essential similarity between encephalomyelitis and multiple sclerosis. In 1941 Putnam³⁶ expressed the view that the origin of encephalomyelitis is in some sense an allergic reaction, adding that "it seems not unreasonable to suppose that an instability of the clotting mechanism of the blood might be one aspect of allergy."

Shortly before this, Baer and Sulzberger⁷ studied the role of allergy in a small group of patients with multiple sclerosis. Their conclusion in part was: "Of our thirty patients with multiple sclerosis who were completely studied, ten, or 33 per cent, presented evidence of personal or familial atopic disease or positive wheal reactions to skin tests or both."

There are many reports in the literature, and we have all seen patients with neurological symptoms produced by allergy. Urbach and Gottlieb⁴⁶ stated: "Paralysis of cerebral origin simulating vascular lesions may be due to angioneurotic edema of the brain caused by injection of foreign serums, as well as by internal absorption of allergens." Brickner¹² observed that: "Often a patient with multiple sclerosis, if pressed, may be able to recall a fleeting symptom years before, such as numbness of the fingers which disturbed his writing for perhaps an afternoon. On a basis of these mild, vague and transitory symptoms one is not justified in making a diagnosis of multiple sclerosis, but a prognosis of this disease should be considered." On this subject Lichtenstein³² says: "The prognosis in multiple sclerosis is not as grave as many would have the profession believe. Some individuals have two or more mild attacks and never go on to develop the advanced form of the disease."

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Dr. Jones is medical director of the Multiple Sclerosis Clinic, St. Joseph's Hospital, Tacoma, Washington.

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In 1940 Ferraro and Jervis,¹⁴ also in 1948 Kabat,^{25,26} Mayer,²⁵ Wolf and Bezer²⁶ reported the production of acute disseminated encephalomyelitis in rhesus monkeys, by the injection of rabbit or monkey brain or monkey spinal cord as an emulsion.

ALLERGY

Following the report of Horton and his co-workers Wagener, Waltman and Aita²³ in 1944, on the treatment of 102 cases of multiple sclerosis with the intravenous administration of histamine diphosphate, we began the study of the disease on an allergy basis. This approach was made in the same manner as in the study of angioneurotic edema, migraine, bronchial asthma, urticaria or any other allergic condition. Complete histories were carefully taken, all were tested for their sensitivity to foods, epidermals, molds, fungi, pollens and miscellaneous allergens. Elimination diets were used, and careful observations were made as to food offenders.

A thorough survey was made as to the precipitating or aggravating factors with reference to pregnancy and trauma. All patients were studied in relation to their emotional stability.

In all, 152 cases were studied and treated, eighty-seven females and sixty-five males. Their ages varied from fifteen to forty-nine years at onset, with an average age of 29.8 years. All except three had lived most of their lives in the northern half of the United States and Canada. There were nineteen acute cases and 133 of the chronic progressive type.

Many of the patients suffered from several different types of allergy. In some patients emotional upsets, pregnancy, and trauma appeared to be the "trigger" that precipitated the disease.

D-TUBOCURARINE

As previously reported,²⁴ we used d-Tubocurarine in oil and wax,* with muscle re-education, very successfully as an aid in our treatment. This medication relieved tremors, spasticity, incontinence and rigidity in nearly all patients. It was given deep into the muscle in doses that varied from 7.5 mg. every fourth day up to as much as 120 mg. daily. There was a wide range in dosage among patients, the effects in some lasting as long as ninety-six hours, in others only twelve to sixteen hours.

The action of the d-Tubocurarine in oil and wax was startlingly good. This preparation gave prolonged action with constant effects. It gave an immediate feeling of relaxation and comfort to the tense, spastic patients. The first dose often gave them the first comfortable night's sleep they had had in years. Incontinence and frequency of urination were improved or controlled in a very short time in every case. Constipation, the "bugaboo" of multiple sclerosis, was relieved in most patients within a few weeks. Tremors were markedly reduced in all cases. Voluntary movements

*Supplied through the courtesy of the Abbott Research Laboratories.

MULTIPLE SCLEROSIS—JONEZ

previously blocked by spastic rigidity were made possible, and patients were able to move hands, arms, legs and other parts of their body in varying degrees approaching normal. These limbs had previously been paralyzed or uncontrollable through spasticity and tremors.

Some patients were able to go for a month to six weeks without a noticeable return of tremors, muscle rigidity or spasticity. Because of this, patients were able to take vacations from treatment at varying intervals with a good effect on their morale.

We have given over 30,000 doses of d-Tubocurarine in the last eighteen months without a single undesirable reaction. Neither has there been any tendency to habituation in any case. As a matter of fact, the patients all seem to want to decrease their dose as rapidly as possible. This is because the accumulative effect is prone to produce uncomfortable dizziness, slight visual symptoms or other side effects, unless the amount of the drug given is gradually decreased. Also, at certain times after the drug has been administered over a period, there will develop a "stiffness" or lack of power in all four limbs and lower jaw. This condition is relieved by withdrawal of the drug for a week or ten days.

MANAGEMENT

Complete allergy management was the basis of our therapy. Under this therapy allergenic extracts were used as indicated. For the typical "head colds" of multiple sclerosis noted by many writers,^{17,41,39} we use respiratory vaccines.

Nearly all of our 152 cases showed some form of allergic sensitivity. Those with multiple food allergies apparently were more spastic than those with other allergies. It is generally conceded that foods are the worst offenders in cerebral allergies.^{10,12,49,50,51} We did not depend on scratch tests wholly, but also used diet diaries and elimination diets. Carefully observing the effects of various foods from a clinical standpoint, several patients were placed on Rowe's⁴⁰ cereal-free diet with apparently very good results. Focal infections were looked for, and cleared up when possible. Eye symptoms and visual fields^{8,11,16,19,21,48} were carefully checked. Improvement in these was used as an index for our therapy, retrobulbar neuritis being considered an early episode of multiple sclerosis.

If exacerbations can be definitely prevented, the normal tendency of the disease is one of recovery.²⁷ Realizing this, we instructed all patients to avoid chilling,⁴⁴ accidents,¹⁴ over-exertion¹⁵ and emotional upsets.³¹ Female patients were told of the dangers of pregnancy^{20,37} in multiple sclerosis.

The criterion of the success of any treatment of multiple sclerosis should be the prevention of relapses.²³ An attitude of rejection in therapy is easy to develop in regard to this disease.¹⁵ As our study is based on the assumption that allergy is the cause of multiple sclerosis, histamine becomes the medication of choice. Norton²² and his co-workers seem in-

clined to relate any recovery and improvement to vasodilatation in the central nervous system resulting from repeated injections of histamine. On the other hand, Ferraro¹⁵ speculated on the beneficial effects of histamine's being the result of the production of histamine-specific antibodies. Kwiatkowski²⁰ has shown that all living tissue contains histamine except the central nervous system, motor nerves and sensory nerves from special sense organs. This was brought to our attention during a conversation with Dr. Horton. We are of the opinion that the dramatic improvement in acute cases and the improved condition of the chronic cases under histamine therapy is in some way related to this absence of histamine in tissues of the central nervous system. The reason for the effectiveness of this therapy will not be known until research gives us greater knowledge of the biochemical and immunological factors involved.

HISTAMINE

We administer histamine by four different methods: subcutaneous, intravenous, continuous infusion and by iontophoresis. Our patients are given histamine diphosphate intravenously to the point of tolerance. They receive 2.75 mg. of histamine diphosphate in 250 c.c. normal saline daily, and others at times a continuous infusion¹³ of 11 mg. histamine diphosphate in 1,000 c.c. of normal saline at a rate of 30 drops per minute every six hours, alternating with 11 mg. histamine diphosphate in 1,000 c.c. of 5 per cent glucose solution. This continuous infusion is given for periods of twenty-four, and in some cases forty-eight hours. Our best results were in the cases that were able to take the larger amounts. In the cases where histamine had been a failure before coming to us, we believe that too little had been given for too short a time. A number of these patients when given larger amounts responded very satisfactorily. Using histamine, we accomplished two purposes: first, the hyposensitization of the patient to the histamine reactions of allergy; and second, the benefit derived from histamine as a vasodilator, being the most effective vasodilator known on the tissues of the central nervous system.

In our series we have administered histamine diphosphate intravenously over 25,000 times and have had no noticeable reactions.

We found, as did Benson and Horton,⁹ that the pulse and blood pressure are only temporarily affected to a slight degree by repeated intravenous injections of histamine.

The patients were also given .275 mg. per c.c. of histamine diphosphate subcutaneously. The dose beginning at .1 c.c. daily was increased in the usual manner. From a therapeutic standpoint, the same size dose of histamine by the subcutaneous route is ten times more effective than it is by the intravenous.²⁰ Following the release from active treatment, we advise our patients to take histamine subcutaneously once a week for the rest of their lives. This, as a prophylaxis against exacerbations of multiple sclerosis. The usual dose is .5 c.c. of a .275 mg. histamine diphosphate per c.c. of solution.

MULTIPLE SCLEROSIS—JONEZ

Recently Abramson^{1,2,3,4,5,6} developed the technique of administering histamine by iontophoresis. This method is very simple, only involving the passage of histamine into the skin, driven by a galvanic current which forms deposits in the pores of the skin. Under the electrode area a large wheal is formed containing histamine, which is slowly absorbed. We believe that this way of administration combines effects of the subcutaneous, intravenous and continuous infusion methods.

The technique employed is as follows: Three folds of canton flannel with 10 c.c. of a 1 per cent solution of histamine diphosphate† are applied to the anterior aspect of the forearm. Contact is then made with the positive electrode which is held in place by an elastic bandage. Canton flannel damp with water, is applied to the other forearm and the negative electrode applied in the same manner. The dosage is controlled by the amount of current used and the length of time of the treatment. We use 2 to 8 milliamperes for fifteen to thirty minutes, according to the reaction of the patient. To overcome hyperacidity, 15 grains of bicarbonate of soda is given by mouth before each treatment.

The principal advantages of histamine iontophoresis are: it is well adapted for home use, the apparatus is inexpensive, and sterile equipment need not be employed. The typical histamine flush occurs within five to ten minutes, and is as intense as that produced by the intravenous method. Absorption from the skin deposits is slow, as the flushed area around the wheal remains from six to seventy-two hours after the treatment.

We do not use iontophoresis until our patients have had at least thirty intravenous injections of histamine. Some had over 200 before starting. Also, only those who have shown marked improvement under intravenous histamine therapy are given the drug by the electrophoresis method. If they continue to show improvement over a period of six to eight weeks, we release them for home treatment.

At this time we are treating sixty-two patients with multiple sclerosis by histamine iontophoresis, twenty-five at home and thirty-seven in the hospital as out-patients. The results have been very satisfactory in all except two cases. These two patients said they felt better under intravenous therapy, so they were returned to that type of treatment. Both of these are wheel-chair cases of long standing. One is very spastic, and the other has a very painful complicating osteoarthritis. All of the other sixty patients appear to improve as well or better under iontophoresis as they had under intravenous histamine.

With histamine therapy in most cases there is a temporary increase in muscular co-ordination and strength. This period of improvement lasts longer with iontophoresis than it does when the histamine is given by the intravenous method.

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MULTIPLE SCLEROSIS—JONEZ

TABLE I. SIXTY-TWO MULTIPLE SCLEROSIS CASES RECEIVING
HISTAMINE IONTOPHORESIS
St. Joseph's Hospital, Tacoma, Washington

Case No. Age Occupation	Allergics	Type	Symptoms On Admission	d-Tubocurarine in oil and wax	Number of Intravenous Histamine Diphosphate Injections	Number of Histamine Ionto- phoresis Treatments	Present Condition
1. Mrs. L.A. 50 H.W.	Urticaria Foods	Ch. Prog. 1933	Spastic Paraplegia Paresthesia Dysarthria Pollakiuria Amblyopia Wheel Chair	7.5 mg. 3 times weekly	131	24 Home treatment after tenth	Walking, symptoms all markedly improved.
2. Miss M.B. 31 Graduate Nurse	Rhinitis	Ch. Prog. 1944	Paresis Euphoria Hippus Strabismus	7.5 mg. 3 times weekly	74	33 Home treatment after tenth	Generally improved.
3. Miss I.B. 35 Office	Neuroedema	Acute	Dysarthria Amblyopia Paresis Pollakiuria	15 mg. 2 times weekly	78	22 Home treatment after tenth	Symptom free.
4. Mrs. M.B. 33 H.W.	Pollens Epidermals	Ch. Prog. 1944	Dysarthria Paraplegia Pollakiuria	15 mg. 3 times weekly	69	36 Home treatment after tenth	Improved.
5. Mr. L.B. 49 Barber	Human Hair Foods	Ch. Prog. 1938	Spastic Paraplegia Cane case 3 years	7.5 mg. 3 times weekly	146	23 Home treatment after fifteenth	Walks without cane.
6. Mrs. M.B. 29 H.W.	Eczema Molds Pollens Foods	Ch. Prog. 1938	Dysarthria Quadriplegia Oscillopsia Pollakiuria Bed-fast	30 mg. 3 times weekly	142	23	Walking in walker wheel chair.
7. Mrs. L.C. 42 H.W.	None	Acute	Paresis Paresthesia Dysarthria Pollakiuria	15 mg. 3 times weekly	30	26 Home treatment after tenth	Symptom free.
8. Mrs. L.C. 43 H.W.	Foods Epidermals	Ch. Prog. 1930	Paraplegia Pollakiuria Amblyopia Wheel chair	15 mg. 3 times weekly	129	22 Home treatment after tenth	Generally improved. Paraplegia same.
9. Mr. F.C. 53 Fruit shipper	Foods	Ch. Prog. 1943	Parasis Dysarthria Oscillopsia Amblyopia	15 mg. 3 times weekly	65	39 Home treatment after tenth	No objective improve- ment.
10. Mrs. M.C. 44 H.W.	Rhinitis Pollens	Acute	Paresis Paresthesia Dysarthria Pollakiuria	15 mg. 3 times weekly	30	12 Home treatment after tenth	Symptom free.
11. Mrs. H.C. 56 H.W.	Foods	Ch. Prog. 1930	Amblyopia Hippus Paresis Strabismus	15 mg. 3 times weekly	72	11 Home treatment after sixth	Objectively symptom free.
12. Mr. R.D. 44 Sheet Metal Worker	Asthma	Ch. Prog. 1944	Spastic Paresis Pollakiuria Paresthesia	30 mg. 3 times weekly	139	15	All symptoms improved.
13. Mrs. R.D. 37 H.W.	Molds	Ch. Prog. 1942	Paraplegia Strabismus Hippus Paresthesia	30 mg. 3 times weekly	112	41 Home treatment after twentieth	Slight general improve- ment.
14. Mrs. L.E. 36 Graduate nurse	Foods Pollens	Ch. Prog. 1944	Paraplegia Amaurosis Dysarthria Pollakiuria	22.5 mg. twice daily	187	36 Home treatment after ninth	No objective improve- ment.

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**TABLE I. SIXTY-TWO MULTIPLE SCLEROSIS CASES RECEIVING
HISTAMINE IONTOPHORESIS**
St. Joseph's Hospital, Tacoma, Washington

Case No. Age Occupation	Allergies	Type	Symptoms On Admission	d-Tubo- curarine in oil and wax	Number of Intravenous Histamine Diphosphate Injections	Number of Histamine Ionto- phoresis Treatments	Present Condition
15. Mr. R.E. 42 Druggist	None	Ch. Prog. 1941	Urinary inconti- nence. Hippus Spastic Paresis	30 mg. 3 times weekly	158	27 Home treatment after tenth	Symptom free.
16. Mr. C.F. 41 Paper- maker	Newspaper	Ch. Prog. 1944	Amblyopia Dysarthria Spastic Paresis all limbs Cane case	30 mg. 3 times weekly	134	39	Generally improved. Walks without cane.
17. Mr. C.F.* 46 Grocer	Foods	Ch. Prog. 1941	Spastic Paresis all limbs Dysarthria Amblyopia	30 mg. 3 times weekly	64	24 Home treatment after tenth	Slight improve- ment.
18. Miss P.F. 42 Seamstress	Epidermals Molds	Ch. Prog. 1944	Hippus Spastic gait Pollakiuria Paresthesia	15 mg. 3 times weekly	96	47	Marked improve- ment. Gait nearly normal.
19. Mr. F.G. 40 Steam Engineer	Foods	Ch. Prog. 1942	Urinary incon- tinence. Spastic gait. Paresthesia.	15 mg. 3 times weekly	203 Continuous infusion 48 hours, 8 sessions.	34	Objectively symptom free. Gait normal.
20. Mr. J.G. 56 Farmer	None	Ch. Prog. 1930	Quadriplegia Urinary incon- tinence. Strabismus Wheel Chair.	30 mg. daily	148	3 Returned to Intra- venous.	Slight objective improve- ment.
21. Mrs. A.H. 36 H.W.	None	Ch. Prog. 1946	Spastic gait Paresthesia	15 mg. 3 times weekly	56	2	Improve- ment in gait.
22. Mrs. D.H. 36 Office	Foods Pollens	Ch. Prog. 1931	Amblyopia Dysarthria Diplopia Paresthesia Spastic gait	15 mg. 3 times weekly	96	45	Objectively symptom free. Gait normal.
23. Mr. J.H. 29 Estimator	Epidermals Foods	Acute	Paresthesia Dysarthria Diplopia Spastic gait	22.5 mg. 3 times weekly	49	33	Objectively symptom free.
24. Mrs. E.H. 29 H.W.	Rhinitis	Ch. Prog. 1941	Paraplegia Euphoria Amblyopia Wheel chair.	22.5 mg. 3 times weekly	186	13	Slight objective improve- ment.
25. Mr. G.H. 67 R.R. worker	None	Ch. Prog. 1918	Dysarthria Spastic Paresis Strabismus	15 mg. 3 times weekly	30	20	All symptoms improved.
26. Miss M.J. 49 Officer	Foods	Ch. Prog. 1940	Spastic Quadriplegia Urinary inconti- nence. Amblyopia. Bed fast.	30 mg. twice daily	173	21	Inconti- nence relieved. Wheel chair. Marked improve- ment.
27. Mrs. A.J. 32 H.W.	None	Acute	Diplopia Dysarthria Spastic gait.	15 mg. 3 times weekly	36	52 Home treatment after tenth	Symptom free.

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28. Mr. C.K. 40 Druggist	Epidermals Molds	Ch. Prog. 1943	Amaurosis Dysarthria Hippus Spastic Quadriplegia Urinary inconti- nence. Wheel chair.	30 mg. 3 times weekly	221 Continuous infusion 24 hours twice. 48 hours once.	39 Home treatment after tenth	Inconti- nence improved markedly. Some im- provement objectively in all other symptoms.
29. Mrs. A.K. 24 H.W.	Rhinitis Pollens	Ch. Prog. 1946	Spastic Quadriplegia Dysarthria Diplopia Wheel chair	15 mg. twice daily	127	26 Home treatment after eleventh	Improve- ment all symptoms. Walks in walker
30. Mrs. V.K. 26 H.W.	Foods Epidermals	Ch. Prog. 1939	Paresthesia Spastic Paresis all limbs	15 mg. 3 times weekly	167	29	Objectively symptom free
31. Mrs. C.K. 32 H.W.	Foods Rhinitis	Ch. Prog. 1941	Amblyopia Dysarthria Spastic Quadriplegia	22.5 mg. daily	138	40 Home treatment after tenth	Slight improve- ment
32. Mrs. B.L. 38 Teacher	None	Ch. Prog. 1944	Paresis Diplopia Paresthesia	15 mg. 3 times weekly	76	2	Slight improve- ment
33. Mrs. E.L. 48 H.W.	Foods	Ch. Prog. 1933	Spastic Quadriplegia Diplopia Wheel chair	30 mg. twice daily	147	35 Home treatment after tenth	No objective improve- ment
34. Mrs. S.L. 42 H.W.	None	Ch. Prog. 1941	Pollakiuria Spastic Paresis Amaurosis	15 mg. 3 times weekly	102	6	Marked improve- ment pollakiuria
35. Mr. W.M. 37 Office	Heat	Ch. Prog. 1940	Paresis Strabismus Spastic gait	15 mg. daily	96	16	No objective improve- ment
36. Mrs. A.M. 18 H.W.	None	Acute	Paraplegia Urinary incontinence. Strabismus Amaurosis Bed-fast	30 mg. twice daily	132	32	Marked improve- ment all symptoms. Walking unassisted.
37. Mr. F.M. 43 Woodsman	None	Acute	Retrobulbar neuritis. Vision: right 20/400 left 20/160	none	32	3	Vision: right 20/30 left 20/40
38. Mr. E.M. 36 Salesman	Pollens Rhinitis	Ch. Prog. 1942	Spastic gait Dysarthria	15 mg. 3 times weekly	81	4	Slight objective improve- ment
39. Mr. E.N. 54 Office	Foods	Ch. Prog. 1941	Hemiplegia Dysarthria	15 mg. 3 times weekly	30	11	Marked improve- ment
40. Mr. O.R. 34 Automobile mechanic	None	Ch. Prog. 1931	Spastic paraplegia. Pollakiuria Paresthesia Amblyopia Wheel chair	30 mg. 3 times weekly	167	37	All symptoms improved
41. Mr. R.O. 48 Lumber- man	Pollens	Ch. Prog. 1939	Spastic gait. Diplopia Hippus Paresthesia	15 mg. 3 times weekly	30	15 Home treatment after tenth	Gait nearly normal

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Case No. Age Occupation	Allergies	Type	Symptoms On Admission	d-Tubo- curarine in oil and wax	Number of Intravenous Histamine Diphosphate Injections	Number of Histamine Iontophoresis Treatments	Present Condition
42. Mrs. H.O. 36 H.W.	Molds Epidermals	Ch. Prog. 1939	Spastic Quadriplegia Wheel chair	15 mg. 3 times weekly	66	46 Home treatment after tenth	Slight objective improve- ment
43. Mrs. C.P. 40 H.W.	None	Acute	Paraplegia Diplopia	15 mg. 3 times weekly	143	35	Symptom free
44. Mr. I.P. 55 Laborer	Rhinitis	Ch. Prog. 1931	Spastic gait Paresis Pollakiuria Amblyopia	15 mg. 3 times weekly	224	29	Gait improved
45. Mr. A.R. 47 Machinist	Molds	Ch. Prog. 1940	Spastic gait Paresis Pollakiuria Amblyopia	15 mg. 3 times weekly	78	46 Home treatment after tenth	Improve- ment all symptoms
46. Miss M.R. 23 Office	Foods	Ch. Prog. 1944	Spastic Paraplegia Pollakiuria Oscillopsia	15 mg. 3 times weekly	81	44	Slight objective improve- ment
47. Mr. J.S. 40 Woodsman	None	Ch. Prog. 1943	Amblyopia Pollakiuria Dysarthria Spastic Paraplegia	15 mg. twice daily	304	11 Returned to intra- venous	Improve- ment in all symptoms
48. Mr. N.S. 53 Hydro- electric worker	Foods Molds	Ch. Prog. 1928	Spastic Hemiplegia Pollakiuria	15 mg. 3 times weekly	163	32	Slight improve- ment
49. Miss B.S. 44 Book- keeper	None	Ch. Prog. 1943	Diplopia Spastic gait	15 mg. 3 times weekly	129	39	Objectively symptom free
50. Miss A.S. 46 Teacher	Hay fever	Ch. Prog. 1939	Diplopia Dysarthria Phresis Pollakiuria Spastic gait	7.5 mg. 3 times weekly	137	52	All except gait, improved
51. Mr. W.S. 40 Office	Rhinitis	Acute	Paresthesia Paresis Amblyopia Spastic gait	15 mg. 3 times weekly	52	26 Home treatment after twenty- second	Objectively symptom free
52. Miss G.S. 44 Telephone Operator	Eczema Epidermals	Ch. Prog. 1941	Spastic Paresis all limbs Pollakiuria Amblyopia Cane case	15 mg. 3 times weekly	182	13	Marked improve- ment all symptoms. Does not use cane.
53. Mrs. G.S. 55 H.W.	Foods	Ch. Prog. 1924	Spastic gait Paresthesia	7.5 mg. daily	151	52	Some objective improve- ment
54. Mr. F.S. 53 Engineer	None	Ch. Prog. 1936	Strabismus Anurosis Spastic Quadriplegia Bleph-	30 mg. twice daily	178	24	Slight improve- ment Wheel chair

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Case No. Age Occupation	Allergies	Type	Symptoms On Admission	d-Tubo- curarine in oil and wax	Number of Intravenous Histamine Diphosphate Injections	Number of Histamine Ionto- phoresis Treatments	Present Condition
55. Mrs. L.W. 38 H.W.	Foods	Ch. Prog. 1941	Hemiplegia Dysphasia Amaurosis. Complete incontinence; Bed-fast.	30 mg. twice daily	78	30	Walks unassisted
56. Mrs. M.W. 28 H.W.	Molds	Ch. Prog. 1946	Spastic Paresis Dysarthria Pollakiuria	15 mg. 3 times weekly	168	39	All symptoms improved
57. Mr. J.W. 39 Office	Asthma Eczema Hay fever	Ch. Prog. 1941	Spastic Paraplegia Paresthesia Pollakiuria Wheel chair	30 mg. 3 times weekly	207 Continuous infusion 48 hours. Six sessions	45	Stands alone. Walks on crutches. All symptoms markedly improved
58. Mrs. M.W. 34 H.W.	Foods	Ch. Prog. 1943	Amaurosis Dysarthria Very spastic Quadriplegia Bed-fast	30 mg. twice daily	153	26	Walks with assistance
59. Mrs. G.W. 56 H.W.	Rhinitis	Ch. Prog. 1930	Paraplegia Paresthesia Pollakiuria Wheel chair	15 mg. 3 times weekly	104	52 Home treatment after thirtieth	Walks by holding to furniture
60. Mr. S.W. 39 Lumber- man	None	Ch. Prog. 1939	Quadriplegia Urinary incontinence. Amaurosis Dysarthria, Bed-fast	15 mg. twice daily	130	65	All symptoms improved. Wheel chair
61. Mr. M.W. 61 Yeast- maker	Molds	Ch. Prog. 1925	Urinary incontinence. Spastic Paraplegia Wheel chair	7.5 mg. 3 times weekly	156	58 Home treatment after tenth	All symptoms improved
62. Mr. F.Z. 49 Tel. Co.	Rhinitis Foods	Ch. Prog. 1940	Spastic Hemiplegia Pollakiuria	15 mg. 3 times weekly	104	44 Home treatment after thirtieth	Marked improve- ment

COMMENTS

The regimen of treatment as outlined has resulted in improvement in a large majority of the patients at our Multiple Sclerosis Clinic. This is spectacularly true in the acute cases. Of these, we have treated nineteen, only one showing no improvement. All of the others became objectively symptom free in a short time. There has not been a major exacerbation among these patients. The remissions at this time have lasted from three months to over two years.

The 133 with chronic types have not responded as dramatically as the acute ones. However, nearly all who have remained under treatment for

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three months or more have shown improvement in varying degrees. As is to be expected, some of these chronic patients become discouraged and stop treatment in a few days or weeks if no marked improvement is noted. However, the more or less mass treatment in our clinic tends to increase the morale of the patients in general. While one may not be improving as rapidly as hoped for, they see others progressing and this keeps their spirits up. Thereby, those who improve act as an inspiration on the others. d-Tubocurarine in oil and wax has been of great value in helping build morale, as it quickly helps in the control of spasticity, tremor and incontinence. By simple orthopedic procedures and muscle re-education, the effectiveness of d-Tubocurarine is increased in the chronic cases.

Tabulating the results of our treatment up to date, we find the following:

Objectively symptom-free, returned to normal activity.....	25
Marked improvement objectively, remained on full employment.....	13
Improved objectively, activities limited.....	37
Slight improvement objectively.....	29
Improved subjectively.....	28
No improvement subjectively or objectively.....	12
Worse than at the beginning of treatment.....	3
Died, since treatment started.....	5
TOTAL	152

The object of therapy in multiple sclerosis is the prevention of exacerbations. When a definite allergy can be shown, it is obvious that this should be eliminated. The difficulty is that in most cases there is more than one allergic offender. It is not possible in each case to determine every substance which can produce a reaction. For this reason even careful allergy management must have an over-all adjunct to prevent relapses in this disease. In our cases, histamine is that agent. There have been practically no major and very few minor exacerbations among our patients who received this therapy regularly. To this end, iontophoresis provides an easy, safe and effective method for the administration of histamine in the home of every sufferer from multiple sclerosis.

CONCLUSIONS

1. Under allergy management and histamine therapy the exacerbations of multiple sclerosis are reduced as to number, and the remissions are lengthened as to time.
2. Following the establishment of a definite diagnosis of multiple sclerosis, some form of histamine therapy is indicated for the balance of the patient's life.
3. The earlier treatment is started, the more successful it is. In the acute cases, the chances of early and long extended remissions are good.
4. In the chronic cases, varying degrees of improvement occur while

under treatment; the improvement appears to continue as long as the patient continues treatment.

5. Treatment as given at our clinic does not cure, but merely arrests symptoms, as is in the case of any other allergic condition. However, it does hold out hope to the patients for their future. By this regimen we have made ambulatory or wheel-chair cases out of bed-fast ones. Also, we have taken wheel-chair patients and made them ambulatory. Still others have become symptom free and remained so without an exacerbation up to periods of over two years. In doing these things for these patients we feel that much has been accomplished.

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DISCUSSION

CHAIRMAN ORVAL R. WITHERS: We will now have the discussion of Dr. Jonez' paper, and I am sure we will all be glad to hear what Dr. Horton, who has done a good deal of work along this line, will have to say about it.

DR. BAYARD T. HORTON: I am personally very glad that Dr. Jonez has brought up the subject of multiple sclerosis, even in the American College of Allergists. Perhaps some of you think it is out of place here, but I for one think that mul-

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tiple sclerosis represents an allergic disease, and furthermore, I am inclined to think that it presents the biggest challenge in this College at the present time.

It is a challenge for the medical profession. Multiple sclerosis is one of the most common diseases affecting the central nervous system and it is far more common than poliomyelitis. As I have said before, we will require a March of Dollars—not the March of Dimes—in approaching this problem.

I feel reasonably sure—and many others agree with me—that we as physicians see only the patients who do not make spontaneous recoveries. This is certainly true of poliomyelitis. Many patients have it in a mild form and recover and never see a physician. The same thing is true with multiple sclerosis.

Two weeks ago I had lunch with one of the professors of neurology in the East, and he expressed that same thought. There are certain fundamental facts which all physicians must keep in mind when thinking and dealing with such a complex problem as multiple sclerosis. In the first place, it is a demyelinating disease, and there are many others, other than multiple sclerosis.

But the two facts I would like to emphasize that are important are as follows:

In the nerve tissue, nerve elements in the central nervous system do not regenerate. For example, if a nerve cell is injured to the point that it dies, or if one of the fibers breaks, the nerve cell does not grow back nor does the broken fiber grow back together. What happens? The supporting structure in the central nervous system is the neurocele. It is comparable to connective tissue on the outside of the central nervous system, and so neurocele plays the predominant role in producing signs and symptoms of most central nervous system diseases, and the neurocele grows in to take the place of nerve elements that die or fibers that are broken.

But the scarred tissue in the central nervous system won't transmit nerve impulses, and therefore the patient with multiple sclerosis gets well but it is a question as to whether he gets well with or without scar formation. It is the same principle that is applied to the cornea. If an individual has an ulceration on the cornea, it may heal with scarring or without scarring. If it heals with scarring, you have an opaque tissue which you try to see through. You can't do it.

So in the central nervous system, it is not a question of healing when the patient dies. He does not die of multiple sclerosis. He dies of something else and when you do the post-mortem examination, you find scarring and you have healing, but that is the challenge to the medical profession. Prevent scarring in the central nervous system and your individual comes back to normal.

The second important fact, I wish to emphasize is that the central nervous system is enclosed in a bony cavity and there is little or no room for expansion. Hence, a little edema will produce a maximal amount of disturbance when it affects the central nervous system, whereas on the skin you call it hives or giant urticaria and do not think much about it. It is this second fact that produces so many dramatic signs and symptoms.

I saw two patients yesterday morning—one a young woman from New York City. Last week I saw her totally blind in the right eye, and the next day she had normal fields and normal vision. You think it can't happen, but it does. It happens many, many times.

The other patient was a young man who had been in the Navy and who had normal vision, but for some unknown reason he went blind. His visual fields were coming back to normal. So keep in mind the fact that there is no regeneration, and secondly, remember that an edema exists which will produce symptoms out of all proportions to what you might expect.

Finally, early diagnosis and early attempts at treatment are of paramount importance. If you wait until the individual has scarring in the central nervous system, you will never change that clinical picture. It is impossible to do so. Don't be

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afraid—one has to lose his sense of fear in approaching the problem of multiple sclerosis.

It is a tremendous field and an allergic disease with which you are dealing, and it should be—and I hope it will be—a challenge to you when you go back home to face these problems. Dr. Jonez, I am very happy to say, has lost his sense of fear, and he is pushing ahead, and don't throw stones at him because it is not justifiable.

CHAIRMAN WITHERS: Is. Dr. Boshes here? Will you continue with the discussion?

DR. LOUIS D. BOSHES: It is indeed an honor for me to be on this rostrum, particularly after hearing and seeing Dr. Horton again, and it is a privilege to discuss this most interesting paper of Dr. Jonez' on multiple sclerosis. Thus far, this has been a hopeless disease, and we neurologists who treat these patients welcome any research on that which will throw light on management. As to the author's components, our observations, however, are not entirely in keeping with those of the author and I will take these up one by one.

We agree that patients with multiple sclerosis may have allergies, but the question is: do these allergies cause lesions in the central nervous system exactly as in the multiple sclerosis? To my knowledge, according to my reading and observations, they do not. In fact, in one of the author's references, I reviewed carefully the work of Rosenow with streptococcal bacterial injections. He admitted the cause of death in animals was obscure, in those that died after the streptococci were no longer isolated in the brain or blood and were no longer demonstrated in the pathological areas. Lesions he produced with inoculated streptococci did not look like the classical picture seen in typical multiple sclerosis.

As to the work mentioned by the author with d-Tubocurarine in oil suspension, we, like many others, have repeated the work of Schlessinger of Columbia, who was one of the first to use this mixture in the treatment of spasticity in multiple sclerosis. In his words, he reported improvement in function and relaxation of involved extremities, lasting up to three to five days following an injection of .5 to 2.5 c.c. of the solution, and he stated, "Spasm, spasticity and rigidity are affected in order of decreasing efficiency."

In the Department of Nervous and Mental Disease of Northwestern University various members took up work with d-Tubocurarine in the Paraplegic Service of the Veterans Hospital in Hines, Illinois, where several paraplegics were put on this preparation; and at the meeting last year of the Chicago Neurological Society, my brother stated there was no release of spasticity at all. Other patients with multiple sclerosis were evaluated, such as these, elsewhere. A typical group of research men, and I will name them—Nathanson and Lesser and Dresser—reported their own work as well as that of others in the *Archives of Neurology and Psychiatry* of June, 1948, and stated that no improvement was offered in active motion, passive motion or functional use in spastic diseases due to the involvement of the central nervous system.

In a group of twelve multiple sclerosis cases on the Neurological Service of Dr. Autff and myself at Cook County Hospital, we repeated the classical work of Schlessinger and arrived at conclusions that there were no beneficial effects. In fact, Donald Monroe of the Boston Harvard Medical School, using distilled water as controls, reported similar effects were reached.

There is no drug known, including even the latest one you have read about in the *Journal of the American Medical Association*—Parpanit, which is a synthetic atropine-like drug with few side actions—that can control the tremor of cerebellar origin such as we see in multiple sclerosis. It is physiologically impossible to control

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spasticity of limbs by drugs and to control the bladder at the same time. That is a neurological paradox.

In general, the author's study is based on the assumption that allergy is the cause of multiple sclerosis. In proof, we hope this would be true because if that were so, all studies could be in that direction and we would be very happy to go along with that.

As far as the vasodilating drugs are concerned, we know of the oral and parenteral ones. No clear-cut long-time beneficial effects have been reported in the use of the oral medications. You all know the work of Dr. Horton, I am sure. Although histamine is the most valuable of the vasodilating drugs, there is no critical proof contrariwise that this drug is an aid in multiple sclerosis. Actually, as the reports come through, more and more there is proof to the contrary.

It is important to remember that the disease has spontaneous remissions, which Dr. Horton has mentioned. Retrobulbar neuritis, in a case which was presented to you a few moments ago, usually clears up with no treatment. Some cases usually subside spontaneously and may not ever appear again. Most cases go untreated anyway and are permitted to lie around. Any treatment is of aid for a while, especially if the patient gets physiotherapy at the same time. Many nonparalyzed, atrophic and weak muscles become functional again by being "used again."

In conclusion, the consensus of the country is that there is no treatment for multiple sclerosis as yet. We must seek for some stabilized treatment to prevent relapses—not in the expectation that myelin will be regenerated or scar dissolved. We hope the allergists will continue their search in that direction.

However, the rigid criterion for improvement used by neurologists must also be used by allergists. It has been a pleasure, indeed, to review the paper by the author and to hear Dr. Horton.

CHAIRMAN WITHERS: Differences of opinion cause us to have more discussion, so we will continue. Dr. Abramson, would you like to make a few remarks?

DR. HAROLD A. ARRAMSON: I think that this difference of opinion is of importance and should be discussed openly because of the rather pessimistic remarks of the preceding speaker. Dr. Boshes stated that there was a consensus of opinion through the country on rigid criteria concerning the therapy of multiple sclerosis as far as neurologic opinion is concerned. I'm afraid that I must disagree with the statement that there is unified opinion amongst neurologists. Even if what Dr. Boshes said is true, that there is a consensus of opinion, I doubt that he can speak for all of the neurologists in the country or for the "rigid criteria" in a disease as complicated as multiple sclerosis. Or should I say in *the diseases of multiple sclerosis*? Let me tell you why.

When I heard Dr. Horton speak at the Pennsylvania Hotel in New York last year, on his technique of administering histamine intravenously in multiple sclerosis, I was very much impressed by the fact that in this hopeless disease, Dr. Horton had developed a method that had a fair theoretical background, was reasonably good psychotherapy, and also had pharmacologic rationale behind it. It appeared to me that it was worthwhile trying. However, against the administration of histamine was the difficulty of giving it intravenously for sixty to ninety days or more. As you know, I have had a fair amount of experience in electrophoresis, and about a year ago I developed a method of giving histamine by electrophoresis so that the rate of administration would be equivalent to the intravenous drip. As Dr. Jonez has pointed out, he has used this method and found the pharmacologic and physiologic effects which I noted. When the blood pressure dropped to 90/50, I expected the patient to collapse. In the majority of the cases, rather than collapse, there was increased muscular co-ordination. That is, instead of having the patient

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with a low blood pressure become weaker, he got up and walked a good deal better. It might be that this is only psychotherapy. However, the severe flush and the change in blood pressure make me feel that to call the reaction psychotherapy, with the profound pharmacological changes readily visible, is possibly adopting the hopeless position that Dr. Boshes has in regard to histamine therapy in multiple sclerosis. I don't feel on the basis of my experiences that the situation is quite so hopeless. As you know, psychotherapy is inherent in *all medical procedures*. There is no justification for allowing a technique to be untried merely because the possibility of psychotherapy is present. Between Dr. Jonez and myself there are about 100 cases which have been treated by this method.

I should like to point out that there are no rigid criteria which can immediately be employed as to whether a drug is efficacious or not. I have had the good fortune to work with Dr. Brickner in New York, and although he is vigorous in his refusal to accept the final value of histamine therapy without further experiment, I do feel that he is more optimistic in the value of testing various drugs, including histamine, under appropriate conditions.

There is an idea that if you wait long enough in multiple sclerosis, you will certainly get a remission. Neither Dr. Jonez or myself wait for remissions; we think that is too dangerous. In the last six to eight months, with the fairly large number of patients under home and out-patient therapy, there have been no marked relapses, if any, in this group. On the other hand, there have been some unexplained phenomena. For example, in patients on home therapy for about six months, a certain amount of lassitude may set in. They are then removed from histamine therapy for a week or two with a remarkable increase of energy.

I should like to ask Dr. Jonez if he has made any physiological observations on the blood. Does the electrophoretic method form deposits? I believe that it does. I have detected secondary flushes following electrophoretic therapy. On the other hand certain other patients do not flush easily. I do not know why.

CHAIRMAN WITHERS: I am breaking a few rules about the minutes that we are using for these talks because this is an important paper and because there is a great deal of interest in it. Is there anyone else who wants to add to the general discussion?

DR. ROBERT J. BRENNAN: With all due respect to the neurologists, I am just a country boy trying to get along in this work, and I think a lot of allergists take the same attitude toward this histamine treatment that a lot of general practitioners take against allergy. If we are going to take that attitude toward histamine treatment, that is the same attitude we will get from the general practitioner toward allergy in general.

One important point that Dr. Jonez brought out is that you have to treat these patients for a long time. Every once in a while some doctor will call up and say he has Mrs. So-and-So in the hospital and that she will be in there for a week, and he wants to know if we will treat her for multiple sclerosis. You can't treat a patient that way. If you are not going to be able to treat them for a couple of months, you may as well not start. That is the way I feel about it.

As to what eventual good you can do the patient, it is hard to say. Recently I had two patients start treatment about the same time. One was a surgical nurse who had been incapacitated a very short time. We treated her about five times a week with the intravenous method, and in about two months she had a very nice remission and has gone along very well on subcutaneous treatment.

The other case was a man who had the disease fifteen years at least—fifteen years that he knew about—and at the time we started treating him he was practically bed-fast. After two and a half to three months of treatment, he is now able to move

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about and drive his own car, and he can talk so that everyone can understand him, whereas originally he was very hard to understand. He is now, as he states it, about seven years better than he was when he started.

He wants to know how long we should keep this up. The way I feel about it is he should just keep it up as long as we can do him any good. This is a sort of hobby with me, and I would advise anybody else to kind of look at it as a hobby, too, because most of these multiple sclerosis cases have been incapacitated so long that if you get back the cost of your materials, you will probably feel like you are doing pretty well. You don't expect to make any money on them.

CHAIRMAN WITHERS: Is there any more discussion?

DR. R. J. MARTORIO: I am in no position to discuss the papers of the previous speakers, but I do like to emphasize the method of Dr. Abramson.

If you have struggled with some of these patients, you will appreciate what Dr. Abramson's treatment means to you. I had struggled with intravenous therapy, and when Dr. Abramson's method came along, I was able to instruct my mother and one of the members in our family on the use of this therapy in the case of my brother who suffers from multiple sclerosis. It is a very simple method and can be used several times a day. You can teach any member of the family how to use this therapy. Personally, I think this is one of the most important advances in the treatment of multiple sclerosis.

CHAIRMAN WITHERS: I guess we will have to stop this now. Dr. Jonez, will you end the discussion?

DR. JONEZ: I will only take a few moments to end this discussion, as we have already far exceeded our allotted time. First, in reply to Dr. Abramson's question regarding histamine blood levels during intravenous and iontophoresis histamine therapy. I know of no way to determine histamine blood levels during either of these methods of medication. In talking with Dr. Ethan Allan Brown this morning on this subject, he stated, "While histamine was being injected intravenously in one arm, blood can be drawn from the opposite arm, and this drawn blood will be perfectly normal, containing no histamine at all." However, we did discover a method of gauging the histamine effect on the blood with reference to the time the effects lasted. We found that in the blood oxyhemoglobin reached a saturation point very shortly after histamine was administered by either method. Following iontophoresis therapy, the increase in oxyhemoglobin lasted in diminishing amounts for about seven hours. By the intravenous method, the oxyhemoglobin level of the blood reached normal in about two hours. This is some indication as to the length of the effectiveness of the two methods of administration of histamine. This increase in oxyhemoglobin also explains the marked blood pressure drop spoken of by Dr. Abramson and the increased metabolic rate during intravenous histamine administration described by Dr. Horton in a paper several years ago.

I do not know whether this increase in oxyhemoglobin has been noted by other workers or not. We have not been able to find any report in the literature on this phenomena. I would like to ask Dr. Horton if he had observed this change in the blood during histamine therapy.

DR. HORTON: Yes, we have made this same observation.

DR. JONEZ: As to Dr. Boshes and our other neurological friends, I feel, as Dr. Horton expressed himself several years ago, that the neurologists have spent many years, in fact over 100 years, in this search, and all the hope and promise that

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they have been able to give these poor unfortunate sufferers was "Get yourself a crutch, then a wheel chair, and after that the bed." We, as allergists, are merely trying to do something to lessen the progress of this disease and help these people, and we do help them.

Dr. Boshes spoke about curare in reference to the work done on twelve multiple sclerosis cases at Cook County Hospital. I call his attention to the fact that the preparation of curare used there is an entirely different one from the d-Tubocurarine we use. We have had several cases come to our clinic who had received the curare spoken of by Dr. Boshes without any noticeable effect before coming to us. When given the d-Tubocurarine used in our clinic, they responded in the same manner that the rest of our cases did. After all, Schlessinger reports the same findings in over 400 cases of various spastic conditions that we found in our 152 cases of multiple sclerosis. He uses the same product of d-Tubocurarine that we do. I think our combined more than 550 cases overshadow the work at Cook County Hospital spoken of today.

As a matter of fact, this preparation certainly does quickly relieve spasticities in all parts of the body. However, should it only give these people a dry bed to sleep in, its use is most assuredly worthwhile.

COTTONSEED PROTEIN VS. COTTONSEED OIL SENSITIVITY

(Continued from Page 14)

2. The refining processes of cottonseed oil diminished the atopen content of the oil slightly, but did not destroy its active principle.

The author wishes to express his appreciation to Dr. Matthew Walzer for his many criticisms and helpful suggestions in the above investigation.

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A STANDARDIZED PATCH TEST

LOUIS SCHWARTZ, M.D.
Washington, D.C.

JADASSOHN devised the patch test in 1895 for the purpose of diagnosing contact dermatitis. At that time there was not the clear distinction which we now make between primary skin irritants and sensitizers.

A primary cutaneous irritant is an agent which will cause dermatitis by direct action on the skin at the site of contact if it is permitted to act in sufficient intensity or quantity for a sufficient time. A primary irritant acts locally by direct chemical, physical or mechanical action.

A cutaneous sensitizer is an agent which may not cause demonstrable changes on first contact, but may effect such undemonstrable changes in certain individuals that after five to seven days or more, further contact on the same or other parts of the skin will cause dermatitis. A cutaneous sensitizer acts systemically through the body fluids.

It is obvious that patch tests with known primary irritants are not diagnostic, unless the primary irritants are so dilute as to have lost their irritant properties, whereas patch tests for diagnostic purposes can be performed with any agent which is not a primary irritant and with which the patient has come in contact. Primary irritants may also be sensitizers, as for instance formaldehyde and the alkaline bichromates. The sensitizing powers of substances vary, some of them being capable of sensitizing a large proportion of those exposed and some only a very small percentage; however, the sensitizing potential of each substance is directly proportional to the amount of the chemical and to the time it remains in contact with the skin.

The resistance of the skin of different persons and of even different portions of the skin of the same person varies to the action of both primary irritants and sensitizers. Where the reactive tissue of the skin is covered with many layers of cornified cells, it requires large quantities of primary irritants, or longer contact, to reach reactive tissue, and such a skin will not be sensitized as readily as a skin the reactive tissue of which is nearer the surface.

Individuals also vary in degrees of sensitivity irrespective of the thickness of the skin. Some are so sensitive that the mere presence of the allergen in the same room will cause them to itch. I've seen workers who were so sensitive to some chemicals with which they had worked, that even going into the vicinity of the factory caused them to break out in a rash. Then again, the degree of sensitivity may vary from time to time.

The patch test as used heretofore has not been standardized. Different dermatologists would use different techniques of applying the patch test.

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Chicago, Illinois.
Dr. Schwartz is an Honorary Fellow of The American College of Allergists.

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Some would saturate a piece of blotting paper of indefinite size and apply it to the skin. Others would use various sized pieces of various plies of surgical gauze, containing indefinite amounts of the liquid or powdered solid. As a result it was often found that one dermatologist could not duplicate or substantiate the results obtained by another.

We know that the reaction to a patch test depends on (1) the degree of sensitivity of the patient, (2) the concentration of the substance applied, (3) the amount of the substance applied per square centimeter of skin, and (4) the length of time that it remains in contact with the skin.

In performing a diagnostic patch test, we have heretofore controlled the time the patch has remained on the skin, and in some instances we have known or controlled the concentration of the irritant; but we have not definitely controlled the amount of the irritant nor the area of skin to which it was applied.

Because of this, the results by different observers have varied. Some, using small amounts of allergens on larger areas of the skin, have obtained slight or no reactions on patients who showed marked reactions when larger amounts were used by others.

All these facts have led to devising a method of patch testing by which definitely known amounts can be applied to a constant area of skin, for definitely known periods, all of which can be recorded and stated when the reactions are read.

The proposed standard patch consists of (1) a square piece of flannel measuring 3 sq. cm. which becomes saturated with 0.2 c.c. of a liquid, (2) a pipette graduated so that measured amounts varying from 0.05 to 0.2 c.c. can be applied to the flannel, (3) a square piece of uncoated regenerated cellulose 1 to 1½ inches on each side, used for insulation, and (4) a piece of elastoplast of a special shape measuring 3 inches across the diagonal. The piece of cellulose is adhered to the center of the elastoplast and the piece of flannel is attached to the center of the cellulose. If it is desired to patch test with a liquid the concentration of it must be known and a definite amount placed on the flannel. The patch is then applied to the skin, and permitted to remain on for a definite period.

The result is written as follows:

Substance	Site	Concentration	Solvent	Amount	Area	Time
Amm. Thioglyco. Reaction	R. forearm Delayed Reaction	5%	Water	0.15 c.c.	3 sq. cm.	24 hrs.
Amm. Thioglyco. Reaction	L. forearm Delayed Reaction	10%	Water	0.15 c.c.	3 sq. cm.	24 hrs.
++	+					

The relative sensitivity of different subjects can also be determined by placing patches of similar concentration on them and noting the degrees of the reactions.

Thresholds of sensitivity can be determined by placing various amounts of the same concentration or the same amount of various concentrations on the same subjects.

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The relative sensitizing powers of chemicals may be determined by placing patches of similar concentrations of each chemical on several hundred subjects, allowing them to remain on for the same definite period and repeating the procedure ten to fourteen days later and noting the number of subjects sensitized by each substance and the degree of the reactions.

The sensitizing properties of solids can be determined by dissolving definite amounts in a suitable solvent, applying 0.2 c.c. of the solution to the 3 sq. cm. piece of flannel and allowing the flannel to remain on a porcelain or glass surface until the solvent evaporates. This procedure will deposit on the flannel an evenly distributed known amount of the substance to be tested. The dry patch can then be applied.

If it is desired to use larger amounts of the sensitizing chemical, higher concentrations of the solution can be used; or if this is not possible, after the solvent has evaporated from the flannel, 0.2 c.c. of the solution can be reapplied to the flannel and the solvent can again be permitted to evaporate, thus leaving on the flannel double the amount of solid. This procedure can be repeated as often as desired, tripling, quadrupling, et cetera, the amount of solid dispersed on the flannel.

Ointments can be tested by spreading definite amounts over the surface of the 3 sq. cm. piece of flannel.

The kit consists of the prepared patches and a graduated pipette or dropper which permits the application of the desired amount of liquid to the flannel. (A hypodermic syringe having a small calibre may also be used to measure the amounts of liquid.) If larger pieces of flannel are desired, they can be cut, but the areas of the pieces must be known and recorded so that results can be evaluated.

When liquids are used for patch testing, they sometimes spread, covering the area of skin under the insulating cellulose; this happens if pressure is applied on the patch at the site overlying the wet flannel. Therefore, in applying the patch, pressure over this site should be avoided by pressing on the tabs at the corners of the patch in order to make it stick, rather than pressing on the center. However, the liquid does not spread beyond the cellulose insulation because the plaster adhering to the skin at the borders of the cellulose prevents spreading.

The adhesive is spread on a square piece of elastoplast and the patch cut so that it has a tongue at each corner, on which slight traction can be made in applying the patch. The procedure practically gives the patch the property of a two-way stretch.

SUMMARY

A new patch test device is described which permits the performance of comparable and standard patch testing.

915 15th Street N. W.

SKIN TESTS WITH STEROID HORMONES IN ALLERGIC DISEASES

MARY-KATHARINE HAJOS, M.D.

Budapest, Hungary

THE publication by Doctors Baer, Witten and Allen, "Skin Tests with Endocrine Substances," in the May-June, 1948, issue of *ANNALS OF ALLERGY*, recorded dermatological cases. We performed the same tests according to Zondek and Bromberg's method for well over a year at the Medical Department of the Apponyi Polyclinic, Budapest. As the majority of our patients suffered from allergic asthma, I would like to add our own results in the study of endocrine allergy.

Hormone solutions in olive oil vehicle (prepared for us in the G. Richter chemical laboratories, according to Zondek's indications) were as follows: desoxycorticosterone acetate, progesterone, pregnadiol, estrone, testosterone, androsterone. Aqueous solutions of glanduatin and insulin served for testing only in case of evident sensitivity with these substances.

Subjects for our tests were carefully chosen from among allergic patients, whose allergic manifestations were closely related to the sexual cycle, i.e., premenstrual tension, menstruation, pregnancy, preclimax, climax. The total number of cases thus tested amounted to 107, out of which twelve adults—males and females with nonallergic complaints—and four children served as controls to check the specificity of our results.

Diagnosis of allergic subjects with suspected hormone sensitivity was as follows:

Total number of suspected cases: 79 female, 12 male.

Bronchial asthma.....	63
Urticaria, eczema.....	13
Pruritus	2
Hyperthyroidism + asthma.....	2
Obesity	6
Climax	4
Keratitis rosacea.....	3

Positive reactions were as follows:

	Female	Male
Progesterone	25	12
Pregnadiol	11	
Estrone	10	
Testosterone	8	2
Androsterone	7	4
Desoxycorticosterone	6	
Neohombreol		1

Olive oil and cholesterine had been used for controls, with positive results twice with olive oil, and once with cholesterine, without hormone sensitivity. Control cases never proved to have positive reactions. The evaluation of male subjects has to be treated carefully, as results were neither characteristic nor convincing. The only conclusion we attempt to reach is the observation of sensitivity in male subjects under forty years of age to male hormones and over forty, to female sex hormones.

Other observations are as follows:

1. In cases of allergic manifestations associated with the sex cycle, hormone testing proved to be more or less positive.
2. Hypersensitivity to various hormones at the same time is, regardless of the sexual character of the hormones, in question. Simultaneous positive reactions with progesterone and androsterone, testosterone and estrone—as occurring most frequently—may be explained by the well-known fact that testosterone may possess progesterone-like properties, while progesterone occasionally simulates androgenous effects.

CASE REPORTS

Case 1.—Mrs. G. I., aged thirty-four, had been treated previously with glandubolin (Estrogenic substance, sec. G. Richter) because of menstrual disorders. She developed severe urticaria after the fifth injection. The eruptions persisted about a week after administration of the hormone. When her urticaria subsided, and menstrual complaints as regards irregular periods did not improve, another hormonal treatment, first with syntestrin, then with glandubolin, was attempted. Following the first injection of glandubolin, urticarial eruptions flared up. She was then hospitalized and treated first with the usual methods. When her urticaria had subsided, we performed our hormone testing, with the result of sensitivity to estrone and pregnadiol. Intradermal tests with glandubolin elicited severe local and generalized symptoms. Treatment was started with small doses of estrogenic hormone, with complete disappearance of symptoms after a two-month course.

Case 2.—Mrs. K. B., aged twenty-seven, had her first eczematous symptoms after an abortion two years ago. Since then her periods have been irregular, and she has noticed intermenstrual flare-up of eczema. As checked by hormone-level calculations, we found the exacerbations to occur approximately at the time of ovulation. The hormone tests showed sensitivity to all female sex hormones. Treatment with small doses of estrogenic hormone improved her complaints.

Case 3.—Mrs. H. H., aged fifty-seven, came with ocular allergic complaints. Hormone testing gave positive results with estrone. She had previously undergone a treatment of syntestrin and glandubolin. Small doses of these hormones improved her symptoms.

Case 4.—Mrs. P. J., aged fifty-three, had been treated for bronchial asthma for twenty-two years. Her menstrual history disclosed that she had never menstruated at all. Testing her with hormones, she presented elective progesterone sensitivity of a very high degree. The local reaction subsided for over a month, and flared up during several cycles substituting menstrual cycles. Treatment with small doses of prolucon improved her asthmatic manifestations.

We still continue our studies in endocrine allergy, but in our subsequent tests we are going to emphasize the correlation of hormone sensitivity to hormone levels in the organism and changes of the vasomotor nervous system. We wish to extend our investigations in tests for thyroxin-sensitivity as well.

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Museum Krt. 39

THE PARENTERAL USE OF NEO-ANTERGAN

A Clinical Study

JEROME MILLER, M.D.

Philadelphia, Pennsylvania

NEO-ANTERGAN, an effective histamine antagonist, has been shown to possess antihistaminic, anti-anaphylactic and wheal-reducing properties. Comparative clinical studies of the antihistaminic activity of various drugs administered orally revealed Neo-Antergan to be equal to or greater than most histamine antagonists.^{2,3,4,5,6,8,11,12,13,14,16,17} Since the parenteral administration of Neo-Antergan has not been reported in the human, it was deemed advisable to investigate and report its clinical effect. Neo-Antergan Maleate,* a brand of pyranisamine maleate (N' -p-methoxybenzyl- N' , N' -dimethyl-N-a-pyridylethylenediamine maleate), was used throughout the experiment.

PROCEDURE

Neo-Antergan was administered to a group of 138 patients during the summer and fall of 1948. The series comprised patients suffering from seasonal and perennial hay fever, asthma, urticaria, atopic dermatitis, migraine, and allergic conjunctivitis. The drug was administered either by the intravenous or intramuscular route. Each cubic centimeter contained 10 mg. of Neo-Antergan Maleate. In order to determine the optimum dosage the drug was administered in amounts varying from 2 to 15 mg. The average dose was 4 to 5 mg. The patients were not selected and consisted of cases obtained from private practice and clinic. There were fifty-seven males and eighty-one females, ranging from eight to sixty-seven years of age.

Neo-Antergan was used concurrently in patients receiving coseasonal desensitization and in those cases that did not obtain 50 per cent relief from the perennial or preseasonal method of desensitization. It was administered parenterally during the pollinating season at the time the patient was manifesting symptoms, regardless of the concentration of the pollen in the atmosphere. Normal saline, a placebo, was used as the control. Patients claiming relief from Neo-Antergan had normal saline substituted and its effect noted. The relief obtained was based upon the patient's subjective statements, and corroborated by the findings in the eyes, nose and chest.

In order to determine the time that elapsed for the drug to take effect, the duration of relief, and the side reactions, each patient received one to six injections. Laboratory studies included complete blood count, urinalysis and electrocardiogram. Urine specimens and blood counts were taken before treatment and two to four times during the course of the survey.

Chief of Allergy Department of the Skin and Cancer Hospital on the Temple University Medical School Service.

*Furnished through courtesy of Merck and Co., Inc., Rahway, N. J.

TABLE I. TYPES OF ALLERGIC CONDITIONS RECEIVING NEO-ANTERGAN

Seasonal hay fever	
1. Co-seasonal	41
2. Perennial and preseasonal with less than 50% result	31
Perennial allergic rhinitis	28
Bronchial asthma	14
Atopic dermatitis	6
Urticaria and/or angioneurotic edema	12
Migraine	4
Allergic conjunctivitis	2
Total	138

TABLE II. SYMPTOMATIC RELIEF PRODUCED BY NEO-ANTERGAN

Diagnosis	No. Cases	No. Improved	% Improved
Hay fever	72	46	63.8%
Perennial allergic rhinitis	28	18	64.0%
Bronchial asthma	14	4	28.5%
Atopic dermatitis	6	2	33.0%
Urticaria and/or angioneurotic edema	12	8	66.0%
Migraine	4	1	25.0%
Allergic conjunctivitis	2	0	0.0%

RESULTS

The intravenous method produced severe drowsiness, almost to the point of stupor. Other patients complained of pressure symptoms in the chest, perspired freely, became dyspneic and developed wheezing respirations. The intravenous method was therefore discarded in favor of the intramuscular route.

The relief of symptoms from the parenteral administration of Neo-Antergan, usually occurs within ten to thirty minutes. The duration of relief varies from one to ten hours, with an average of four to five hours. Table II indicates the symptomatic relief obtained following the parenteral administration of Neo-Antergan.

The best results were obtained in patients suffering from seasonal and perennial hay fever and urticaria. In the hay fever group it relieved the sneezing, itching of the eyes and nose, severe rhinorrhea, and cleared the nasal passages. Substitution of a placebo in the form of normal saline for the antihistaminic drug failed on repeated occasions. Upon reintroducing Neo-Antergan, the patient obtained symptomatic relief.

A favorable response was obtained in urticaria and angioneurotic edema. Its antipruritic effect was fairly rapid and pronounced. The massive swellings diminished in size and at times disappeared. The rapidity of relief was equivalent to that of epinephrine, without producing the palpitations, tachycardia, pallor and nervousness. The effect of Neo-Antergan at times was more prolonged than epinephrine, and its sedative effect an added point in its favor. Upon discontinuing the drug, the symptoms recurred, and were once again relieved with its re-introduction. In a proper evaluation of results, it must be remembered that acute urticaria is a self-limited disease. In chronic urticaria, the lesions tend to recur.

The results in bronchial asthma were somewhat disappointing. In two patients, the asthma was precipitated or aggravated by the administration of Neo-Antergan. In those cases of hay fever that progress to asthma, Neo-Antergan also fails to relieve the distressful respiratory symptoms.

Atopic dermatitis does not respond favorably to Neo-Antergan. The antipruritic effect was noteworthy, but since the syndrome continued unabated the results were recorded as unimproved. Its importance is in the sedation that is afforded the patient at night, which prevents the trauma and secondary infection incident to the scratching.

Only one patient with migraine improved. The remaining three were unaffected. Two patients with allergic conjunctivitis did not respond to parenteral Neo-Antergan. While the number of cases is too small to warrant conclusions, the results are consistent with those of other observers.

Urinary analysis revealed no abnormalities. Hematologic determinations were all within normal limits. The electrocardiograms revealed no abnormal cardiac physiological changes.

Side reactions occurred in thirty-two of the 138 cases. The type of side reaction is listed in Table III.

TABLE III. SIDE REACTIONS WITH NEO-ANTERGAN

Side Reactions	No. of Cases
Drowsiness	39
Dizziness	7
Dry Mouth	5
Dry Nose	4
Tinnitus	2
Weakness and Fatigue	2
Abdominal Cramps	1
Asthma	2

A total of sixty-two undesirable effects were noted in the thirty-two cases. Drowsiness seemed to occur far in excess of the other untoward reactions. One patient who was driven to her place of employment was found asleep at her typewriter. Other reactions noted are dizziness, dry mouth and nose, tinnitus, weakness and fatigue, abdominal cramps, dyspnea and aggravation or precipitation of the asthmatic attack. The potential danger of these reactions, particularly the soporific effect, becomes quite apparent. The undesirable effects seem to appear more frequently when Neo-Antergan is given intravenously. The side reactions increase in proportion to the amount of the drug that is used.

DISCUSSION

The parenteral administration of Neo-Antergan is only a palliative procedure. It may be used concurrently in those patients not receiving adequate relief from specific therapy. Clinically, Neo-Antergan is a valuable adjunct in the symptomatic treatment of hay fever. This procedure, however, will not prevent the progression of hay fever to the asthmatic state. The results obtained are comparable to those of Bernstein,¹ who found that oral Neo-Antergan relieved 65 per cent of patients suffering from hay fever.

The results obtained in urticaria are in accord with those of Waldbott.¹⁵ Koelsche¹⁰ reported 74 per cent relief in patients having hay fever and asthma. However, only one-third of the 74 per cent obtained relief of the associated asthma. Waldbott also states that asthma responds less favor-

ably to the antihistaminic drugs than does hay fever. He therefore suggests that there is a more pronounced antiwhealing than bronchial inhibiting effect. Henderson and Rose⁹ report similar results in migraine with Pyribenzamine. Friedlaender and Friedlaender,⁷ using Pyribenzamine, report failures in migraine and vernal conjunctivitis.

Many patients suffering with some form of allergic disorder are not benefited by or cannot tolerate oral medication. It is in this group that the parenteral administration of Neo-Antergan is of distinct value. Its duration of action as compared with epinephrine is a point in its favor. The undesirable tachycardia, palpitation and nervousness produced by epinephrine is avoided. The sedative action of Neo-Antergan may be desirable at times. It does not however warrant replacement therapy of epinephrine, the iodides, aminophylline or the sympathomimetic drugs.

The incidence of relief and the side reactions were compared with the results of other observers using various antihistaminic agents. The degree of relief and the percentage of side effects tend to run parallel with the other histaminic antagonists. The vagaries of the allergic state at times made it difficult to properly evaluate the duration of relief.

SUMMARY

1. Neo-Antergan, an antihistaminic drug, was administered intravenously and intramuscularly to a group of 138 cases.
2. It was found to be very effective in the relief of symptoms of seasonal hay fever, perennial allergic rhinitis and urticaria.
3. It is of questionable value in bronchial asthma, atopic dermatitis, migraine and allergic conjunctivitis.
4. Side reactions occurred in 23 per cent of the cases.
5. Urinalysis, blood counts and electrocardiograms were relatively normal.
6. The incidence of relief tends to run parallel to the other antihistaminic drugs, as reported by various investigators.
7. It has an apparent potential advantage in that it may be administered parenterally.

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ALLERGIC TOXEMIA AND FATIGUE

ALBERT H. ROWE, M.D., F.A.C.A.
Oakland, California

IN 1927 allergic toxemia in children due to pollen was reported by Kahn.¹ Soon after, the writer realized that food allergy was a much more common cause and in 1930 published a paper on Allergic Toxemia* due to Food Allergy.² Fatigue, weakness, lack of energy and ambition, drowsiness, lassitude, bodily aching, depression, irritability, fever, chilling and night sweats were reported in varying combinations and degrees. Since then we have continued to report these symptoms from food and less so from pollen allergy. In 1936³ statistics on twenty-nine relieved patients were published. Moreno in Buenos Aires has written five articles on the toxemia³ since 1940, and one additional excellent article has appeared in American literature by Randolph⁴ in 1945. Recently Mariante⁵ has reported on this syndrome.

All other possible causes of fatigue and these other symptoms must be ruled out, including infections, new growths, metabolic, vascular, blood and endocrine disturbances and mild or definite insanities. Today there is a vogue of ascribing fatigue and related symptoms to "benign nervousness" or psychosomatic causes, as found in articles by Allan, Portis and others. When present-day and traditional examinations and tests have been negative, or treatment based on positive findings has failed, I agree with Randolph that this diagnosis is not justified unless allergy also has been excluded by proper and adequate study. The demonstration of other diseases or pathologic conditions, moreover, does not exclude concomitant allergic toxemia. Without the recognition of this allergy, patients unjustifiably may be stigmatized as psychoneurotic or even psychotic, often being left to cope with their disabling symptoms alone.

Fatigue and weakness due to allergy may be most evident in the mornings, even after a long night's rest or sleep. Patients hate to get up or may find it difficult to awaken. Often this fatigue continues throughout the day. One patient said, "I'm so tired I wonder how I get through the day." Another stated, "I get tired and achy doing nothing." Some have to lie down most of the time. This fatigue may increase in the late afternoon and evening, causing sleep, drowsiness and inability to concentrate mentally after dinner. With the control of the allergy, these results disappear. One relieved patient stated that now she is anxious to work, formerly having forced all mental and physical effort. She can accomplish much at home, even in the evening, which she "hasn't been able to do for twenty years."

Loss of energy, mental confusion and drowsiness probably due to cerebral allergy often are associated with the fatigue. This leads to inefficiency, impaired accomplishment and ambition. These symptoms, along with irritability, tenseness, depression and at times emotional instability, produce

*Drug allergy also produces many of the symptoms of this allergic toxemia and fever.

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TABLE I. ALLERGIC TOXEMIA AND FATIGUE IN 70 PATIENTS*

Average age	42 (10-70)	Per cent
Male	28
Female	72
Duration of toxemia	9.4 years (1-40).	
"Toxic symptoms"		
Fatigue	94
Not rested on arising.....	57
Lack of energy.....	66
Aching in joints.....	47
Aching in muscles.....	36
Aching in chest.....	10
Listlessness, drowsiness.....	37
Disability in concentration.....	27
Confusion	17
Depression	30
Irritability	20
Nervous tension.....	34
Emotional instability	6
Insomnia	11
Fever	10
Night Sweats.....	3
Chilling and gooseflesh.....	3
Tachycardia	10

*All of these patients were relieved of their various symptoms by the elimination of allergenic foods. All other possible causes were studied by the writer or by referring physicians. Several patients had been to 6 to 12 and one to 18 physicians. Psychiatric and psychosomatic study and treatment had been resorted to by 8 patients.

Many other patients with other various manifestations of food and inhalant allergy had mild or moderate fatigue and other symptoms of this toxemia. Moreover many patients with severe sick headache preceded or associated with fatigue and exhaustion were not included. Finally the many patients with ulcerative colitis, due in our opinion fundamentally to food, and at times to pollen allergy, in whom marked exhaustion, fatigue and depression and other symptoms occurred, were omitted.

changes in personality that may be recognized by the patient but are uncontrollable. When these allergic symptoms occur in children, their true cause usually is overlooked. Thus a boy of two and one-half years was seen two years ago because of "head colds" with listlessness, drowsiness and lack of energy since birth. These symptoms had been exaggerated every week or two with fever up to 104°F. for two to four days. Drowsiness or sleep often continued for three to four days. In the second year fever decreased but perspiration for days at a time developed. Physical and mental activity was retarded. "He just sat. He never wore out his shoes." Doctors, including a psychiatrist, opined that he was subnormal mentally and probably would never go to school. All of these symptoms, except slight drowsiness every few weeks, have been absent with an elimination diet in the last twenty months. He is energetic and alert. Shoes are worn out in two months.

Other children become sullen, obstinate, incorrigible, have bursts of temper or cannot adjust themselves to other children. School work suffers. With the control of allergy a normal personality gradually is established and maintained.

Thus a girl of seven years had had "sinus attacks" every four to six weeks for four years, associated with cough and fever from 101° to 105°F. for a week or more. She was constantly lifeless and unwilling to play, saying she felt "like a rag doll." Nervousness and fatigue interfered with school work. "She frequently was naughty, had tantrums, and was impossible to control." Her appetite was poor. She refused to eat for most of her six years. Doctors had been consulted with no benefit.

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TABLE II. ALLERGIC TOXEMIA AND FATIGUE IN 70 PATIENTS

Manifestations of allergy other than toxemia	Per cent
Fever.....	63
..... nuchal pain).....	50
Eczema	10
Hives and swellings.....	16
Hay fever	9
Nasal allergy.....	34
Bronchial asthma	6
Urogenital allergy	4
Epilepsy and petit mal.....	3
Family history of allergy	
Bronchial asthma.....	23
Nasal allergy	9
Hay fever	11
Eczema	7
Hives and swellings.....	7
Headaches	17
Gastrointestinal symptoms.....	19

With the cereal-free elimination diet, improvement was noted in two weeks, "and she was a different child in four weeks." Normal energy and a "spring in her step" developed. She ate all the time, taking second helpings, eating between meals and saying "I am sure hungry," instead of "I don't like that old stuff." "She attends school all day, comes home full of energy, rakes leaves, climbs trees and keeps going until ten o'clock at night." Nervousness and a tendency to crying ceased. She has been at the top of her class and has been chosen to represent her class in a school play.

Dreams, nightmares and restlessness during the night may occur. Insomnia, especially on retiring or after 1:00 to 4:00 a.m., may be present in infants and children and especially in adults.

Aching and soreness in the joints, tendons and muscles often result from allergic reactivity, especially from foods. At times this is confined to a few joints or to limited areas such as the low mid-back, the nuchal or shoulder areas or extremities. Food allergy along with bacterial and other allergies needs consideration as one cause of incipient or established rheumatoid arthritis, the allergic nature of which is indicated by the collagen and other tissue and joint changes described especially by Rich. Several encouraging results in rheumatoid arthritis as well as in chronic or recurrent tendo-synovitis have justified our study of food allergy along with its other allergic and generally considered causes.

At times, fever, chilling, and sweating apparently occur in varying degrees from food allergy. Resultant vascular allergy probably accounts for the hypotension and tachycardia which often arise from food and other allergy. Food allergy, together with inhalant, bacterial and the demonstrated drug and serum allergies, also need to be studied in periarthritis nodosa, the allergic nature of which is recognized.

All of these symptoms may vary in degree. As in other manifestations of food allergy, such as asthma or recurrent headaches, this toxemia may occur in cyclic attacks. Usually it is persistent, exaggerated at regular intervals especially in women during their periods. Because of the beneficial effect of the summer and also inland, dry areas on food allergy, long reported by the writer, allergic toxemia may decrease in these months and in such regions. Exaggeration of symptoms during the spring, summer and

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TABLE III. ALLERGIC TOXEMIA AND FATIGUE IN 70 PATIENTS

	Per Cent
Skin testing	
Pollens	20
Animal emanations.....	11
Dusts	10
Miscellaneous inhalants.....	11
Foods	21
Roentgen ray studies of gastrointestinal tract negative in.....	27
Roentgen ray studies of gall bladder negative in.....	23
Stomach analysis negative in.....	16
' Achylia in.....	4
Positive dietary history.....	40
Causes	
Food allergy	93
Food and pollen allergy.....	1
Pollen allergy alone.....	6

fall occurs in toxemia due to pollen allergy. Other manifestations of allergy, especially cerebral, gastrointestinal, and nasal occur in these patients, varying in numbers as shown in Table II.

PATHOGENESIS AND PATHOLOGY

The pathogenesis of this syndrome is not known. Randolph⁴ has reported atypical mononuclear cells resembling those found in infectious mononucleosis in patients with allergic toxemia. Other evidence of systemic disturbance is lacking. Chronic allergy, especially to foods, does not produce recognized changes in the blood except leukopenia after ingestion of allergenic foods, reported especially by Vaughan. Eosinophilia is not usual. The sedimentation rate has been increased in some of these patients in the absence of any demonstrable cause other than chronic food allergy.

The symptomatology depends on the tissues affected by the allergic reactivity. Vascular allergy is known to produce vascular inflammation, increased permeability and local edema. The possibility of collagen disturbances, the maximum evidence of which has been demonstrated by Rich and others in periarteritis nodosa, has to be considered in patients with severe long standing allergic toxemia.

Information from tissue biopsies in these patients would be of great interest, but the good prognosis in co-operating patients does not justify this study. The absence of fatalities in these patients allows no post-mortem examinations.

DIAGNOSIS AND CONTROL

Food allergy should be suspected when these symptoms of toxemia are present, and especially if other manifestations of food allergy, enumerated in Table II, are evidenced in the history.

A dietary history of dislikes or disagreements for foods suggests but does not affirm allergy as a specific cause. Specific questions should be asked, such as, "Do you like milk, eat eggs, fish or fruit?" Thus patients may state that they hate milk, or that it is a poison, or that it causes vomiting, or pain in various parts of the abdomen, or asthma. One patient found it made her "sick all over and tired for a week." Another was certain that

fatigue developed in two or three hours from milk even in very minute amounts. Egg, fish or fruit allergy often is evidenced in the history. One of my patients has found that grapes as such, or in wine or even vinegar, produce allergic toxemia.

Skin testing is of little help. When the patient knows that immediate and severe reactions occur to specific foods, reacting bodies may be in the skin, as shown by the positive scratch reactions and by a positive Prausnitz-Kustner reaction. But when clinical symptoms from food allergy are delayed for a few hours or are accumulative, appearing in one or two days after the ingestion of the food, the skin reaction usually is absent. Too often, small or even definite reactions to foods, especially by the intradermal method, indicate past or potential allergy or are nonspecific. Positive skin reactions, moreover, must be confirmed by reproduction of symptoms in the symptom-free patient from the ingestion of the specific food.

Thus diet trial becomes our most important diagnostic measure. In some patients the exclusion of foods indicated by dietary history or by large scratch reactions gives relief. This usually fails, especially when symptoms are due to the cumulative type of food allergy. This has justified the use of our elimination diets with their detailed menus and recipes for bakery products.

The writer's cereal-free elimination diet⁷ usually is ordered for the initial study of possible food allergy in these patients. If improvement is not evident in two or three weeks, then the fruit and cereal-free elimination diet may be utilized. This fruit-free elimination diet, moreover, is used for initial diet trial if the dietary history indicates probable fruit allergy. If no relief develops in another two or three weeks and food allergy still seems likely, a minimal elimination diet may be tried, such as one containing lamb, white potato, tapioca, sugar, noniodized salt and water, with vitamins A and D in a relatively nonallergic form such as Provital, and calcium carbonate 1/3 to ½ teaspoonsful doses daily. This diet can be prepared to contain 60 to 80 grams of protein and 2,000 or more calories each day. When relief with any of these elimination diets is assured, individual foods are added, one every four to seven days, excluding any which reproduce symptoms. However, if a diet is producing relief of long standing chronic symptoms, especially if chronic tissue changes exist as in allergic arthritis, the relieving elimination diet should be continued for weeks or even months, always with definite assurance that nutrition requirements are being satisfied.

The necessity of absolute exclusion of disallowed foods and the prescribing of the elimination diet with menus and directions so that nutrition and weight are maintained require constant emphasis. It requires more than a few days for the allergens of previously eaten foods to leave the body and especially for the cellular changes resulting from long existent chronic food allergies to decrease or disappear.

Pollen allergy is indicated by history, more successfully by skin testing

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than in food allergy, and finally is confirmed by beneficial pollen desensitization. Other inhalant allergy, which at times causes allergic toxemia, as evidenced by reports of Rinkel and others, and by our own observations, requires similar study and treatment, as discussed above for pollen allergy.

If drug allergy is suspected, total or prolonged exclusion is the answer.

For the symptomatic control of the manifestations of allergic toxemia, epinephrine, hypodermically, may be tried. The antihistaminic drugs in our experience will not control the chronic severe symptoms. They help the mild ones, especially those arising in patients on proper diets who unwittingly or against orders break their diets. Histamine therapy rarely is of help. Aspirin or acetamine gives temporary relief. Allergy at times to many drugs and toxic reactions or allergy to the antihistaminic drugs must be remembered.

SUMMARY

Allergic toxemia or fatigue due to food allergy was first reported by the writer in 1930 and since then by Moreno and Randolph.

It produces fatigue, weakness, lack of energy, and ambition, drowsiness, loginess, bodily aching, depression, irritability, restless sleep, insomnia, fever, chilling and night sweats in varying combinations and degree.

Pollen and also drug allergies are less frequent causes.

Food and less often other allergies must receive adequate study along with other possible infections, metabolic, vascular and endocrine diseases, new growths and true psychoses before these patients are stigmatized as psychoneurotics suffering with "benign nervousness." In children this fatigue is often associated with nasal or bronchial allergy, especially from foods, producing recurrent so-called "colds," with or without asthma, and frequently associated with fever and sweating due to food allergy rather than infection.

In adults such fatigue, bodily aching, depression, nervousness, doppiness and the other symptoms of this toxemia may be so active that actual work in business and the home, or efficiency therein, is impossible.

The control of food allergy nearly always depends on the accurate use of trial diets, for which the writer's various elimination diets, as described in the above article, have been of increasing help during the last twenty years.

CASE HISTORIES

Brief summaries of the following cases of allergic toxemia show the varying symptoms of this syndrome which may occur. Other manifestations of clinical allergy (Table II) may or may not be present. Because of space, negative physical and laboratory findings and negative skin reactions to foods and inhalants are omitted.

Case 1.—A woman of twenty-nine years had been fatigued for four years, spending an increasing time abed. She had been nervous, perspired easily and slept poorly. "Just gets weaker and weaker, and yawns all the time." Her tongue was coated;

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there was pain and soreness in the left abdomen; hemorrhoids and constipation were present.

Dietary history revealed distention from milk, pain in her abdomen for three to four days from egg, and much abdominal distress from fruits.

With the fruit-free elimination diet it was found that her symptoms were relieved and that milk, egg and all fruits, nuts and spices were necessary to exclude for continued comfort.

Case 2.—A woman of thirty-four years had had fatigue, bodily aching, lethargy, emotional instability, nervousness, irritability and much recent depression for two years. Her fatigue was not relieved even with twelve to fourteen hours of sleep. Tachycardia had been present much of the time. Epigastric distention, belching and heartburn had been present nearly continually in the last year. Constipation had occurred two to three days each week. Eczema of the neck had occurred during two winters.

Thyroid and tobacco had been eliminated through the advice of one physician, and several others had been consulted without benefit.

With the fruit-free elimination diets,⁷ symptoms were decreased in two weeks and greatly relieved in one month. In two more months all symptoms, including fatigue, nervousness, tachycardia, indigestion and constipation, were controlled. Weight had increased from 118 to 130 pounds. During the last year this control has continued with the elimination of all fruits and spices, bacon, coffee, pork and no egg or milk as such.

Case 3.—A woman of fifty-nine years had had fatigue, exhaustion and stiffness all over the body for twenty years. The "arthritis" had been severe in the knees, shoulders, lower back and neck, being exaggerated in attacks for days or weeks and increased with exercise. She had pulled herself out of bed for several years. A surgical girdle was worn for fifteen years.

Her arms tired so easily she had been unable even to brush her hair.

Treatment by several doctors including internists had been of no help.

With the fruit-free elimination diet, her symptoms were relieved in two months, and the continued exclusion of milk, eggs, all fruits and spices has been required.

Case 4.—A woman of thirty years, after return from the Philippines seven years ago, developed fever up to 103° to 104°F. for one to four weeks, every six months, increasing to every three to four months. In the last two years fever from 99° to 101°F. had been present daily. Weakness, exhaustion, drowsiness, restless sleep and depression had continued, varying in degree. Generalized aching especially in the hands, fingers and feet had occurred. Headache, especially in the back of her neck and eyes, had recurred every two to four weeks, often associated with nausea and vomiting. Blocking and buzzing of the ears, congestion and tingling in the nose and a lump in the throat had been frequent.

The dietary history revealed a dislike for egg, pork, and fish and fruit increased many of her symptoms.

Her mother had recurrent headaches.

All examinations including studies for known causes of persistent fever had been done by several physicians with no benefit from any treatment.

Skin testing revealed no reactions to important inhalants or foods.

With the fruit and cereal-free elimination diet, all her symptoms were controlled during a two-month period. It has been found that all fruits, fish and corn must be excluded. Corn produces a severe headache in twelve hours. Fruit produces cramps in thirty minutes and dysentery with a dizzy feeling for one and one-half days.

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Case 5.—A man of fifty-seven years first developed aching, soreness, swelling and stiffness in the flexor tendons of the palms ten years ago, with rapid extension to other joints of the fingers, wrists, feet, ankles and elbows. Aching and soreness occurred especially in the mid-thoracic areas of the spine with associated aching around the chest, especially in the cardiac area. The soreness and swelling of the joints had occurred every two to four weeks for five to ten days at a time.

Fatigue, exhaustion, and varying depression had occurred with the above symptoms, increasing in degree throughout the years. He had severe allergic dermatitis from penicillin by mouth and parenterally three times.

Many physicians had sought for foci of infection and gout, hypothyroidism and other possible causes including psychosomatic influences without benefit. The strain of his professional responsibility was blamed.

All symptoms were lessened in inland areas, especially in the summer.

With the fruit-free elimination diet, fatigue, exhaustion, depression and the aching of the body and soreness and swelling of joints were relieved. For continued relief all fruits and spices, squash, pumpkin and milk, as such must be eliminated.

Case 6.—A woman of seventy years was first seen in June, 1946, because of fatigue, generalized aching, weakness and a trembling in her legs, and a "poisoned, slowed down feeling" increasingly in the last ten years. For ten years constipation, distention and a pressure throughout the abdomen, especially in the epigastrium and under the sternum, had increased. At times this distress prevented rest at night, and she feared heart disease. For six months there had been eight to ten watery, non-bloody daily stools with some cramping and much urgency.

Rich, heavy foods, and especially fruits, had increased her abdominal discomfort.

All examinations, including röntgen ray studies of the gall bladder and gastrointestinal tract were negative except for an achylia. Large doses of dilute hydrochloric acid relieved her diarrhea but none of her other symptoms.

With the fruit-free elimination diet, all symptoms of her "toxemia" were relieved in two months. It has been necessary to eliminate all fruits, spices and flavors, milk, wheat and chocolate to maintain control. Though she ate no fruits, her symptoms returned while canning fruits, indicating entrance of the fruit allergens into the body by inhalation.

Case 7.—A man of forty years had had aching and tiredness in the calves for two years. Generalized fatigue and loss of energy had occurred for the last six to eight months, even after nine hours in bed. He forced himself in his work and "wanted to flop in the evening." He had awakened one to three times each night with night sweats. A headache has been present on awakening three to four times a week.

All examinations, including x-ray of his gall bladder, and stomach analysis were negative.

With the fruit-free elimination diet, his symptoms gradually disappeared in five weeks. With the addition of other foods, wheat reproduced his fatigue and aching in the legs. This result has been repeated several times in the last year.

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MERCUHYDRIN SENSITIVITY

Report of a Case

A. H. FINEMAN, M.D., F.A.C.A., and S. J. ROSENBERG, M.D.
New York, New York

In recent years several articles have appeared in the literature dealing with untoward reactions to mercuhydrin and other mercurial diuretics. These reactions have been classified as either toxic or allergic. In the latter group various manifestations have been reported, such as erythematous eruptions, exfoliative dermatitis, urticaria, chills and fever, anaphylactoid shock and even death. Gotlib,⁵ in a recent review of the subject, discussed the allergic nature of these untoward reactions and added one case of his own in a man who received mercupurin and developed generalized urticaria and slight elevation of temperature after the fifth injection. Seventeen days later, following another injection, an immediate and more severe generalized urticaria developed within a few minutes and lasted two to three days. In December, 1948, M. Gelfand⁴ presented a case of mercuhydrin sensitivity in a man who developed chills and fever (103° F.), retrosternal distress and weakness after the fifth intramuscular injection of mercuhydrin which recurred ten days later following another injection.

We wish to add to the literature an unusual reaction of chills and high fever (105.8° F.) associated with a cutaneous eruption and exfoliative dermatitis of the palms of the hands in a woman who received eleven injections before chills and fever first occurred. She subsequently developed an accelerated reaction to injections begun fourteen days later. An immediate reaction ensued within one-half hour after the final injection thirty-two days later. Because of the unusual opportunity afforded us to observe this patient in these three stages of sensitization and because of the infrequent occurrence of such untoward reactions, we felt this case was worthy of report.

CASE REPORT

F. L., a forty-eight-year-old widowed Negress, was admitted to Sydenham Hospital on December 2, 1948, with a history of substernal oppression of two weeks' duration and subsequent dyspnea and orthopnea. Digitalis was taken for one week with little or no relief, and during the five days prior to admission she experienced increasing substernal pressure, hemoptysis, chills and slight fever. The past history was essentially negative. The personal and family history of allergy was also negative. Venereal disease was denied.

On admission the patient was acutely ill, moderately dyspneic with a temperature of 102° F. The pulse was 110 per minute, Corrigan in type; the blood pressure was 136/58. The lungs showed moist râles at the bases posteriorly; the heart was enlarged to the left, and loud systolic and diastolic murmurs were heard over the base transmitted down behind the sternum. A soft systolic and diastolic murmur was also heard at the apex. The liver was felt three to four fingers below the costal margin and was slightly tender. There was some pre-tibial and ankle edema. A diagnosis of congestive heart failure and luetic heart disease with a double aortic lesion

From the Allergy Department and the Medical Service, Sydenham Hospital, Dr. Emanuel Appelbaum, Director of Medicine.

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was made. The patient was given digitalis leaf, 1.5 gr. (0.1 gm.) and ammonium chloride, 30 gr. (2.0 gm.) daily, and also, 2.0 c.c. of mercuhydrin intramuscularly. The condition remained practically unchanged in the first week. The temperature ranged between 101° F. and 99° F.; the moist râles were still present at the bases, and the dyspnea was only mildly relieved. The white blood cell count ranged from 5,100 to 12,500 with a relatively normal differential. The hemoglobin was 67 per cent; the sedimentation rate, 22 mm. The blood urea nitrogen was 19.6 mg. per cent and the total serum proteins, 7.5 mg. per cent. The blood serology was 4-plus with the Mazzini and Kline tests. The blood cultures were negative. The urine showed a trace of albumin and a few hyaline and granular casts and was negative on culture. X-ray of the chest showed marked enlargement of the heart to the right and left, also some evidence of pulmonary congestion.

Because of the low-grade fever and the apical murmurs, concurrent rheumatic heart disease was considered as well as subacute bacterial endocarditis. On the eleventh day after admission the patient experienced a shaking chill and fever, the temperature rising to 102.4° F. The following day she was afebrile. On the thirteenth day another chill and fever occurred, the temperature rising to 105° F. This repeated itself on the fourteenth, fifteenth and sixteenth days, with a temperature of 105.8° F. on the last day. The diagnosis of subacute bacterial endocarditis was more seriously considered but the blood cultures remained negative. At this time it was suggested³ that the chills and spiking temperatures might be due to the mercuhydrin which the patient had been getting intramuscularly daily since admission. The mercurial diuretic was discontinued, and the chills and fever did not recur. From the sixteenth to the thirtieth day the temperature ranged from 99° F. to 100° F. The general condition improved and x-ray of the chest showed marked reduction in the size of the heart. On the twenty-sixth day after admission there developed a pruritus of the palms of the hands which eventually developed into an exfoliative dermatitis and lasted for two to three weeks. On the thirtieth day mercuhydrin therapy was resumed. The same dose, 2 c.c., was given intramuscularly with no untoward reaction. This was repeated on the thirty-first day with no side effect but on the thirty-second day chills and fever occurred, the temperature rising to 105.4° F. On the following day the temperature rose to 102° F. and mercuhydrin was again discontinued. Associated with the chills and fever were dull retrosternal pain and "numbness and burning sensations of the legs." Sensitivity to mercuhydrin was strongly suspected. About a week later there appeared a fine desquamation over the lower abdomen and back and upper thighs. From the thirty-third day after admission to the sixty-fifth day, no mercuhydrin was given and the temperature remained practically normal except for one rise to 102° F. On the sixty-fifth day a much smaller dose, 0.5 c.c., of mercuhydrin was given intramuscularly and close observation of the patient was ordered and carried out. Within one-half hour she experienced tingling sensations all over the body including the lips and tongue, and at the end of one hour she complained of generalized pain involving the upper and lower extremities, the back, and especially, the lumbar region. Soon after, severe headache developed, at first occipital and then frontal. One-half c.c. of epinephrine hydrochloride (1:1000) was given subcutaneously, and second, 1½ grains (0.1 gm.) by mouth. The temperature, pulse and respiration remained unchanged. The blood pressure was unaltered. The patient was watched constantly. She had a restless night and complained of headache and pains in the extremities. In early morning the temperature rose to 100.6° F. but returned to normal that day. No chills occurred. There was marked diuresis, 2200 c.c. of urine within six hours. Fatigue and weakness persisted for three days. Subsequent injections of saline and aminophylline, 1½ grains (0.1 gm.) intramuscularly caused no untoward reactions. She was discharged on the seventy-fifth day, much improved.

Skin tests performed with the scratch method with mercuhydrin, mercupurin and

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salyrgan were totally negative. Intradermal tests were likewise negative. Patch tests with these substances were negative after forty-eight hours and again negative when read two days later. The scratch-patch test recommended by Gottlieb elicited traumatic irritation no different from control patients. Finally, the serum from a patient receiving mercuhydrin for seven consecutive days without untoward reactions was employed for intradermal testing in our patient with negative results. (Leftwich technique). All the above tests were repeated. No positive skin test could be demonstrated in this case to any of the mercurial diuretics with any method of skin testing.

DISCUSSION

There can be little doubt that the chills and fever present in this case were due to the injections of mercuhydrin. The time intervals for the development of these manifestations are of striking significance inasmuch as the symptoms first appeared on the eleventh day in the first course of treatment, on the third day of the second course and within one-half hour after the final injection given one month later. These reactions seem to correspond to the three phases observed in the classical induced form of hypersensitivity, namely, serum disease, and include the initial, the accelerated and immediate reactions. Similar time intervals may occur in sensitization to other drugs, biologicals, chemical agents, antibiotics and other substances. Rarely, however, have all three phases been reported in patients with mercuhydrin sensitivity. In most instances the immediate reactions have occurred at the onset of the second course of treatment. We had the unusual opportunity of observing all three phases of acquired sensitivity in this case.

The most common allergic reactions from the mercurial diuretics are the cutaneous manifestations, such as urticaria, angioneurotic edema, exfoliative dermatitis and erythematous eruptions. While our patient developed an exfoliative dermatitis of the palms of the hands and a desquamation of the lower abdomen and upper thighs, nevertheless, these manifestations were not the predominant side effects.

Other reactions, such as chills and fever and anaphylactoid shock, are less commonly observed but are usually more serious in nature. They are frequently but not always preceded by cutaneous eruptions which should serve as a "danger signal" for further therapy with the mercurial diuretics. It is quite possible that some of the fatal reactions reported might have been avoided if this warning had been taken into account. Discontinuance of the drug is the safest procedure rather than the substitution of one preparation for another.

Skin tests with these drugs are most frequently negative. This is true of drug allergy in general, where symptoms of asthma, urticaria, angioneurotic edema, dermatitis, et cetera, occur from simple chemicals, such as aspirin and aminopyrine, in individuals with totally negative skin tests and with the absence of circulating antibodies. The explanation for clinical sensitivity to drugs in humans, and the failure to demonstrate positive skin reactions, is not fully understood. Most authorities are inclined to apply the

theory of Landsteiner from his work on sensitization in animals with simple nonprotein chemical substances. In a large series of experiments Landsteiner⁶ and his co-workers were able to produce sensitization and anaphylaxis with a nonantigenic substance by combining it with a protein or large molecule. The new conjugated substance specifically sensitized animals and acted as a true antigen. The chemical was regarded as a hapten, and subsequent injections of this substance alone or in conjugated form could produce typical anaphylactic reactions. If this mechanism holds true for human drug allergy, it can explain clinical hypersensitivity to drugs, nonprotein in nature, in individuals with negative skin tests. Enough proof, however, has not yet been established to substantiate this theory.

In our case of mercuhydrin sensitivity, skin tests with the scratch, intradermal and patch methods were totally negative. The scratch-patch test was also negative. Three different mercurial diuretics were used. Burrows and Stokes,¹ however, reported positive patch tests in cases with erythematous eruptions due to the mercurial, neptal. Gottlieb reported a case of a man who developed generalized urticaria from mercupurin and showed positive scratch-patch tests to the drug. Gelfand's case of mercuhydrin sensitivity showed negative intradermal tests but a positive reaction to the Leftwich technique. This test was described by Leftwich⁷ and employed by him as an aid in the diagnosis of hypersensitivity to the sulfonamides. Serum was obtained from individuals taking sulfonamides orally without untoward reactions and used for intradermal tests in patients who manifested drug fever from these agents. Positive reactions were obtained in twenty-eight out of thirty cases, or more than 90 per cent. It is believed that the drug combines with the plasma protein, *in vivo*, forming a complex sensitizing antigen capable of producing a positive skin test. In our case this technique was followed with serum obtained from two mercuhydrin-treated individuals for seven days, and negative results were obtained with both sera. Further studies along these lines with this technique are indicated.

It should be noted that toxic reactions also follow the use of mercurial diuretics. These symptoms are referable to the gastrointestinal, urinary, cardiac and central nervous systems. They are more commonly observed in patients with renal and wasting disease. Several sudden deaths have been reported² following the intravenous administration of these mercurials, and they were attributed to the toxic effect on the heart with the production of ventricular fibrillation. No fatalities occurred with the intramuscular or rectal route of administration.

SUMMARY

1. A case of mercuhydrin sensitivity with chills, high fever and an exfoliative dermatitis is recorded.
2. Skin tests with the scratch, intradermal, patch and scratch-patch methods were totally negative with mercuhydrin, mercupurin and salyrgan. The Leftwich technique was also negative.
3. Hypersensitivity to the mercurial diuretics, while rare, may be se-

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rious in nature and should serve as a warning against further treatment with these drugs.

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2940 Summit Street, Oakland.

ORAL PROCAINE HYDROCHLORIDE THERAPY IN ASTHMA

MARK M. SCHAPIRO, M.D., M.S., and MAX SADOVE, M.D.

Chicago, Illinois

STATUS ASTHMATICUS is defined by Piness as "an asthmatic condition that does not respond to the ordinary methods of treatment."³ The May 29, 1948, issue of the *Journal of the American Medical Association* presents a panel discussion on the available methods of treatment of acute and chronic asthma. All forms of therapy are discussed, with the exception of two methods used almost routinely and with excellent results in the leading clinics abroad. These are the intravenous administration of procaine hydrochloride in normal saline solution and the blocking of the stellate ganglion, vagus nerve and cervical sympathetics with the same drug.¹ The Queries and Minor Notes of the August 21, 1948 issue of the same journal mentions the work of State and Wangensteen,⁴ who used intravenous procaine in the treatment of urticaria and serum sickness with excellent results.

We have surveyed the available literature and cannot find any reference to the use of procaine hydrochloride orally in the treatment of this condition. Because of the dramatic and persistent relief which we obtained in one patient by this method, we feel justified in bringing it to the attention of the medical profession. This is entirely a preliminary report, without any effort being made to explain the result obtained, the pharmacology, physiology, or mechanics of the effect. We believe the action of the procaine may, in reality, be due to its breakdown products, diethenol-amine or para-aminobenzoic acid.

CASE REPORT

The patient, M. F., a white girl, was eighteen years old.

Past History.—Following an attack of pneumonia at the age of two, the patient's mother noticed an increasing respiratory distress which was finally diagnosed by the attending pediatrician as asthma. Various medications were instituted by different doctors over the next six-year period with only slight or temporary relief of the asthmatic condition. The attacks occurred spasmodically, with no seasonal incidence, and were of varying intensity, but were always preceded or complicated by an upper respiratory infection. During this interval, most relief was obtained by the use of epinephrine injections which were given almost every week.

In 1939, she was admitted to the Bobs Roberts Pediatric Division of the University of Chicago Clinics where a complete examination and study were made. Allergy skin tests undertaken at this time revealed sensitivity to feathers, eggs, chocolate, milk, house dust and dog hair. Epinephrine was given by injection and by mouth, but satisfactory results were noticed for only short intervals. After discharge from the hospital she was placed under the care of an allergist who administered autogenous

From the Department of Surgery, the American Hospital, Chicago, Illinois.
Dr. Schapiro was Associate in Surgery, the American Hospital, Chicago, Illinois, at the time this paper was written.
Dr. Sadove is Associate Professor of Anesthesia, University of Illinois College of Medicine, Chicago, Illinois.

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vaccines three times a week. These were discontinued after several weeks when absolutely no relief was obtained and after she developed rather severe local and systemic reactions.

At the age of ten, she again had pneumonia which required four months' hospitalization. At the age of eleven, she was readmitted to the Bobs Roberts Hospital for further study, but no change was noticed in her skin reactions to another series of skin tests.

From this time to 1943, the patient stated that she had only a period of three months' duration in which she was completely free of attacks, and was able to attend school regularly. Since 1943, she has not been free of attacks for longer than forty-eight hours. From 1946 to December, 1947, she was under the constant care of an allergist who gave her specific immunizations, all the present available antihistamine drugs, and the newer antiasthmatic preparations available, with only slight relief at any time. After repeated use of several of the antihistaminic drugs, she developed rather violent drug reactions, manifested by headache, nausea, vomiting, nervousness, skin rashes, et cetera.

Present History.—On December 21, 1947, the patient was seen for the first time by one of us (M.M.S.) in an acute asthmatic attack that had been increasing in severity for over five hours and had not responded to any of the wide variety of available drugs in her stock. She was in extreme distress, leaning forwards in bed, grasping her legs, and gasping for air. Her respirations were so labored that they were audible almost fifteen feet away. The patient was rather deeply cyanotic, her eyes were widely dilated, the nares flared, and the whole chest heaved with every breath. The abdomen was forcibly retracted and every accessory muscle was utilized in breathing. A profuse perspiration was on the forehead and face, the pulse was bounding and could barely be counted. She had received a total of 1.5 cubic centimeters of epinephrine by injection before my arrival. She was given immediately one-quarter grain of morphine followed by a slow intravenous injection of seven and one-half grains of aminophylline. Within a half an hour, definite improvement could be noticed, with a slowing of the pulse, less labored breathing and a lessened nervousness. Another injection of morphine was given and within the hour she fell into a fitful sleep, with decided improvement of respiration.

Between December 21, 1947, and April, 1948, the patient was seen once or twice each week for almost identical attacks, which were not completely relieved by the intravenous administration of aminophylline. The medication varied considerably and included every new drug introduced on the market. As a rule partial relief was obtained from all, for periods lasting from three to seven days, but after this interval, no further relief was afforded by any of the marketed drugs, either alone or in combination. Most were given in maximum doses. During this time, the patient was totally unable to work, was almost always in bed, with the least effort bringing on a severe attack. She lost the appetite that remained, and was deteriorating rapidly both mentally and physically.

It was during this time that the case was brought to the attention of the co-author (M. S.) who suggested the possibility of either an intravenous procaine injection or a stellate ganglion block. Reference was made to the work of Donoso,² who described the mechanism of asthmatic reactions and the etiology of bronchial spasm, demonstrating that novocaine could relieve the constriction and restore the lumen of the bronchi and bronchioles through its antihistamine action. The matter was discussed thoroughly, and we felt that because of the apparent hopelessness of the case, any effort to break the severe bronchial spasm present here should be attempted. The seriousness of the situation was then discussed with the patient and her family, emphasizing the purely experimental aspects of the therapy, the little

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there was to offer, and promising little hope of recovery. The patient was admitted to the American Hospital, April 12, 1948.

Hospital Course.—Physical examination on hospitalization revealed that the heart tones were irregular, definitely stronger on expiration, becoming barely perceptible on inspiration. There was a moderate pulsus paradoxus. Anterior cardiac diameter was enlarged to the right. The lungs revealed numerous sibilant, sonorous and subcrepitant râles over both lung fields, continuous during inspiration and expiration. Laboratory examination was not contributory. X-ray of the chest revealed a generalized pulmonary emphysema, with nodular infiltrations of both apices. Re-examination of the lungs on April 22, 1948, revealed no evidence of an active pulmonary pathologic condition, but no decrease in the emphysema.

One hour after hospitalization, skin sensitivity tests with procaine hydrochloride, 1:1,000 and 1:100 dilutions, using normal saline as control, were performed using the flexor surfaces of both arms. There was almost immediate severe reactions to both dilutions, with a wide area of erythema, a large urticarial wheal with pseudopods and intense itching. A delayed generalized reaction to the skin tests was noted later that same evening when the patient developed a severe asthmatic attack lasting until the next morning. Intranasal oxygen was given, but discontinued since it apparently made her feel worse. The day after the skin test, the patient was so nervous that she required five injections of Demerol (100 mg. each) and was given Trasentine by mouth.

In spite of the skin sensitivity to the procaine solution, it was decided to give her a small intravenous test dose, using a 1:100,000 dilution in distilled water. After eight minutes running time the patient developed an alarming reaction, with a sudden respiratory arrest, intense dyspnea, marked flushing of the face and extreme nervousness. One hundred milligrams of Demerol gave absolutely no relief. The patient would not tolerate pure oxygen by mask. As a last resort 7.5 grains of aminophylline were given intravenously very slowly, with much relief in a short time. One hour after the injection, the patient vomited but seemed to rest comfortably for three and one-half hours.

The entire hospital course was very stormy, requiring an almost constant vigil by one of us or by one of the resident hospital staff. Following the second intravenous injection of aminophylline, the patient developed a shock-like syndrome, with barely perceptible pulse, shallow respirations, unrecordable blood pressure, et cetera. The attending intern remained on constant call and eventually, by using various drugs, brought about recovery. During the stay in the hospital, she was given a course of deep x-ray therapy to both lungs as recommended by some for this condition, but with little relief.

She was discharged thirteen days after admission in fair physical condition, with definitely improved mental state, better appetite, but rather discouraged by failure to perform the proposed block.

Post-Discharge Course.—Because of a sudden pain in the right lower quadrant associated with nausea and vomiting she was readmitted to the hospital on May 19, 1948. Several years previously, she had been told that she had a subacute appendix, but because of her asthmatic condition, the previous physician would not operate. On admission, her pain was localized over McBurney's point, with point tenderness, referred pain, and rebound tenderness. Blood count was slightly depressed, but because of her associated condition, little regard was placed on it. She was put to bed with an ice bag to the right lower quadrant, given no medication, and given nothing by mouth. As her pain did not subside, but gradually increased in severity, with more nausea and vomiting, and a slight increase in the blood count, it was felt safer to interfere in spite of her asthmatic condition.

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Under cyclopropane-pentothal anesthesia (given by M. S.) an appendectomy was performed on May 21. The appendectomy was accomplished with very little difficulty or complications. The anesthetic was very well tolerated and rather readily administered. Except for one very slight asthmatic attack on the first postoperative day, the patient did not have a further single episode. She was ambulatory on the third postoperative day and was discharged from the hospital on the seventh post-operative day.

This complete disappearance of asthmatic manifestations was rather a surprise to us, and we were at a loss to explain the mechanism, but our optimism was not for long, because within one week after discharge, we were advised of a slight attack. As the summer started, the attacks gradually increased in severity, were closer together, but did not become as severe as before the operation. We felt that since prior experience showed poor response to all accepted therapy, and that since it was impossible to resort to either procaine intravenously or a stellate block, something drastic had to be done for this patient to prevent a recurrence of her previous condition. By this time, she had started to gain weight, was eating better than at any time previously, was active and mentally happy. Nothing that we could find in the literature was of any help, so again, after discussing the problem among ourselves, we decided to attempt the use of procaine hydrochloride by mouth. This was purely an experimental measure, since we did not know the correct dosage, the toxic effects on the patient, or the effect on the asthmatic attacks. It was with some hesitation that we prescribed our first oral doses.

On July 15, 1948, the drug was started in doses of 10 grains four times a day, even while the patient did not have an attack. She was seen weekly and observed for toxic manifestations. During this time, she had two slight attacks of asthma which were not relieved by the drug. After ten days the dosage was increased to 12.5 grains four times a day. Later, when it was learned that most of the attacks occurred on arising in the morning, and slightly before retiring, the dosage schedule was changed so that 25 grains were taken before she arose in the morning and 12.5 grains were taken before retiring.

Within three days of this schedule, the patient noticed that there was absolutely no tightness in the chest on arising in the morning and that her breathing during the day was easier. She has had absolutely no attacks of asthma since July 31, 1948. Her appetite has improved 100 per cent, she has gained 35 pounds, has returned to work and does not look like the same patient who entered the hospital. She cannot believe that she has had five months without a single attack. In order to test the effect of the drug, it has been withdrawn on three occasions for a period of seventy-two hours, with an immediate return of respiratory distress, tightness in the chest, and a definite asthmatic attack. This can be aborted by immediately giving the drug by mouth.

We have noted absolutely no side reactions, the blood count remains normal, the lung fields show pulmonary emphysema but no active pulmonary pathology, and the appearance of the patient, her mental and physical well being, attest for the efficiency of the drug.

SUMMARY

A case of intractable asthma has been presented which did not respond to any of the accepted remedies available today. An attempt to abort the asthmatic state by the use of procaine intravenously and by stellate block was impossible because of the patient's sensitivity to the drug. As a last resort, and by a method of therapy not heretofore reported in the literature, the patient was given procaine hydrochloride by mouth with dramatic and

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persistent relief. No explanation is offered as to the mechanism of action of the drug so administered.

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ADDENDUM

When last seen by one of us (M.M.S.) in September 1949, the patient was in excellent health, having only minor abortive asthmatic attacks, usually occurring when she dropped the maintenance dose of procaine hydrochloride by mouth. From the inception of treatment July 15, 1948 to the date last seen, the patient had taken approximately 15,000 grains of procaine without any side effects, abnormal changes in the blood or body fluids, or without demonstrating any abnormality that could be detected by any laboratory means available at the present time.

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ENTERIC-COATED ANTIHISTAMINICS

S. WILLIAM SIMON, M.D., F.A.C.A.
Dayton, Ohio

THE PRESENT series of studies was started before any enteric-coated antihistaminic drugs were generally available. The purpose of this work was not to prevent the absorption of the drug for a period of time but rather to see what effect slower absorption would have on the amount of relief from symptoms, the continuity of relief and the development of side reactions.

It has been frequently noted that as the amount of antihistaminic drug taken per given period of time has been raised, so also were the percentage of patients experiencing side reactions from the drug. Therefore, if less of the drug could be given and symptoms adequately controlled, fewer side reactions might be expected. Certain of the side reactions are undoubtedly due to local irritant action on the gastric mucosa and others to the amount of the drug actually circulating in the blood. By enteric-coating the tablets, no medication comes in contact with the gastric mucosa, and if the amount of drug ingested can be reduced, certainly there would be less in the circulating blood.

Neo-Antergan (Merck), N-p-methoxybenzyl-N', N'-dimethyl-N-a-pyridylethylene diamine maleate,³⁻⁶ was selected since side effects have been encountered in approximately 25 per cent of patients receiving it¹ and it was felt that if enteric coating is of value, it should be effectively demonstrated with this preparation. As Feinberg² stated that, in his experience, Neo-Antergan was of benefit in thirty-nine of sixty patients with hay fever and eight of ten with perennial rhinitis, patients presenting these two conditions were used in this study.

The enteric coating used was composed entirely of cellulose acetate hydrogen phthalate. The coating on regular Neo-Antergan tablets is a conventional sugar-coating. Cellulose acetate hydrogen phthalate differs from other enteric coatings, which are insoluble in acid and soluble in alkali, in that it is dissolved by the action of the enzymes of the small intestine. Tablets coated with cellulose acetate hydrogen phthalate may begin to disintegrate as soon as they reach the small intestine. Delayed-action Pyribenzamine tablets are not coated with cellulose acetate hydrogen phthalate, and their action does not begin until four or five hours after ingestion.

While comparison between enteric-coated and plain Neo-Antergan might have given sufficient data, it was decided to also give each patient one of the other antihistaminics in order that the studies might be even better controlled. These drugs, of course, were not enteric coated.

A complete treatment and questionnaire sheet was kept on each patient.

Dr. Simon is Chief, Allergy Clinic, Brown General Hospital.
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1949, Chicago, Illinois.

ENTERIC-COATED ANTIHISTAMINICS—SIMON

TABLE I. TREATMENT PATIENTS RECEIVED OTHER THAN ANTIHISTAMINES

	No. Patients	Hypo-sensitization		No Treatment
		Preseasonal Treatment	Coseasonal Treatment	
Hay fever.....	19	8	6	5
Hyperesthetic rhinitis.....	12	5	—	7

TABLE II. ENTERIC-COATED NEO-ANTERGAN VS. PLAIN

	No. Patients b.i.d.	No. Patients t.i.d.	No. Patients q.i.d.	Improved	Not Improved	Side Reactions
Enteric coated	31	7	2	29 (96%)	2 (4%)	0
Plain	—	26	5	27 (87%)	4 (13%)	4 (13%)

The information obtained on each of the semi-weekly visits as well as the medication prescribed and its frequency were noted thereon. Those also receiving injections had each specific treatment recorded on a standard form.

Thirty-one patients, nineteen with hay fever and twelve with hyperesthetic rhinitis, were selected. The drugs were not used in the same order more than could be helped, some patients being started on plain Neo-Antergan, others on enteric-coated Neo-Antergan, and others on the various anti-histaminics used.

Patients were continued on one drug for a minimum of five days, ragweed hay fever victims being treated from about August 20 to September 10—there being little change in the ragweed pollen count during this period. Of the nineteen patients with hay fever, eight received preseasional treatment, six coseasional treatment and five no pollen treatment. Of the twelve patients with hyperesthetic rhinitis, five received hyposensitization injections and seven none (Table I). As far as could be determined, no changes were made in environmental exposures over the period of the experiment.

Improvement, in general, meant greatly lessened sneezing, nasal discharge and nasal blockage. With enteric-coated Neo-Antergan, twenty-nine were improved, of whom two with hyperesthetic rhinitis noted only less nasal blockage. One with hay fever and one with hyperesthetic rhinitis noted no improvement. With the plain Neo-Antergan twenty-seven were improved. Of those unimproved, the same two who noted no improvement with the enteric-coated tablets noted none with the plain, and the same patients with hyperesthetic rhinitis noted only improvement in nasal blockage.

Enteric-coated Neo-Antergan was given to all patients twice daily, to seven, three times daily, and to two, four times daily. In six of the seven, no additional benefit was found on increasing the dose, while one patient (with hyperesthetic rhinitis) felt that more of the drug gave added improvement.

Uncoated Neo-Antergan was not satisfactory for continued relief when given twice daily. Twenty-six patients were given three tablets daily, and

ENTERIC-COATED ANTIHISTAMINICS—SIMON

TABLE III. EFFECT OF OTHER UNCOATED ANTIHISTAMINICS ON SYMPTOMS

	Thephorin Thenylene Pyribenzamine				Diatrin Decaprym			Totals
	Histadyl 50 mg.	Benadryl 50 mg.	25 mg.	100 mg.	50 mg.	50 mg.	25 mg.	
No. patients taking medication t.i.d.	1	7	4	7	8	2	2	30
No. patients taking medication q.i.d.	0	2	1	0	1	0	2	6
Total patients taking medication	1	9	5	7	9	2	4	36
Improvement	1	9	4	4	9	2	4	32 (89%)
No improvement	0	0	1	3	0	0	0	4 (11%)
Side reactions	1	3	1	1	3	0	1	10 (28%)

TABLE IV.
ANALYSIS OF PATIENTS REACTIONS TO UNCOATED ANTIHISTAMINICS

	Hay Fever	Hyperesthetic Rhinitis	Total
Improved	20 (95%)	12 (80%)	32 (89%)
Not improved	1 (5%)	3 (20%)	4 (11%)

five received four. If dosage was carried higher, the side reactions overshadowed the additional relief.

On these dosages there were no side reactions from the use of enteric-coated tablets, while four patients (13 per cent) experienced side reactions from the uncoated tablets (Table II).

Twenty-six patients (84 per cent) preferred two enteric-coated tablets daily to three or four uncoated tablets for the following reasons: ten felt their symptoms were better controlled, fourteen received the same amount of relief with less medication, and two had side reactions from uncoated Neo-Antergan but none from the enteric-coated (Table VI).

Seven other antihistaminics were given, some patients receiving as many as three besides Neo-Antergan and others only one. None of these drugs adequately controlled symptoms when taken twice daily. In computing the results, the medication was taken three times daily by thirty patients and four times daily by six. These were the optimum dosages for the particular drug and for the particular patient. Again, an increase in the amount daily over four tablets led to a great increase in side reactions which overshadowed the additional relief.

The following antihistaminic agents were used: Histadyl (Lilly) 50 mg., one patient; Benadryl (Parke-Davis) 50 mg., nine patients; Thephorin (Hoffmann-LaRoche) 25 mg., five patients; Thenylene (Abbott) 100 mg., seven patients; Pyribenzamine (Ciba) 50 mg., nine patients; Diatrin (Warner) 50 mg., two patients; and Decaprym (Merrell) 25 mg., four patients. With this small series no additional information would be gleaned by analyzing each drug separately, so only the over-all results are given for comparison (Table III). Thirty-two (89 per cent) were improved; of these, twenty (95 per cent) hay fever patients were benefited, while twelve (80 per cent) of the hyperesthetic rhinitis patients received some relief. Of the four (11 per cent) who were unimproved, one had hay fever and the other three hyperesthetic rhinitis (Table IV). Side reactions occurred ten times (28 per cent), Benadryl and Pyribenzamine each provoking this effect on three occasions and the others once each.

ENTERIC-COATED ANTIHISTAMINICS—SIMON

TABLE V. PATIENTS PREFERENCE IN ANTIHISTAMINICS TRIED

	Preferred Neo-Antergan (ent.) to Plain	Preferred Neo-Antergan (ent.) to other Antihistaminics
Neo-Antergan (ent.) ..	26 (84%)	20 (65%)
Neo-Antergan (plain) ..	3 (9%)	
Other antihistaminic ..		8 (26%)
No difference	2 (7%)	3 (9%)

TABLE VI. REASON FOR PREFERENCE IN ANTIHISTAMINICS

	Same Result with Less Medication	Better Control	No Side Reactions
Neo-Antergan (ent.) vs. Plain	14	10	2
Neo-Antergan (ent.) vs. other antihistaminics	5	12	3

Comparing enteric-coated Neo-Antergan with the other antihistaminics, twenty (65 per cent) preferred the former, eight (26 per cent) preferred the latter, and three felt that there was no difference (Table V). Of those preferring enteric-coated Neo-Antergan, twelve had better control of their symptoms with it, five obtained the same result with less medication, and three had side reactions with the other antihistaminics but none with enteric-coated Neo-Antergan while obtaining about the same relief with either (Table VI).

In comparing enteric-coated Neo-Antergan with uncoated other antihistaminics, one must take into account the fact that if both were either coated or uncoated, there are many who might prefer some other antihistaminic to Neo-Antergan. This makes the figure of 65 per cent who preferred enteric-coated Neo-Antergan to the other uncoated antihistaminics tried all the more remarkable.

DISCUSSION

On analyzing these results it would seem that an enteric-coated antihistaminic gives as good results generally as the uncoated with certain advantages and disadvantages. Advantages: taken less often, smaller dosage, and fewer side reactions. The effectiveness of the drug rises to a certain level and remains there during the day and the night. Disadvantage: reduced speed of action. The uncoated antihistaminic acts faster—generally in twenty minutes, while the enteric-coated tablet taken on an empty stomach takes about thirty minutes—but with the uncoated the relief lasts only up to three or four hours before the symptoms return. The graph of relief would be one of waves unless additional medication were taken before the effects of the preceding medication had worn off. The enteric-coated graph of relief would rise more slowly but would be maintained as a straight line, gradually declining after six to twelve hours.

No attempt was made to estimate the amount of relief in the patients studied since this is entirely subjective and the excellent results obtained in one patient would be considered as only fair in another. For this reason, no analysis was made on the kinds of hyposensitization given. It is well known that the antihistaminics give more relief in the hyposensitized patient and such was our experience, but again returning to the graph of relief of

ENTERIC-COATED ANTIHISTAMINICS—SIMON

symptoms, such a patient is starting at a higher level (some relief) and therefore would naturally be expected to obtain a higher percentage of relief than a patient who had had no treatment.

In discussing relief, only three symptoms were emphasized because all the patients in the series had these symptoms. Not all were relieved in all patients—even though results were excellent—nor was there any definite pattern, some experiencing more relief of one symptom, such as nasal blockage or discharge, and others, relief of all nasal, eye and mouth symptoms.

While in this series no combination of enteric-coated and uncoated antihistaminics was tried, such might be of benefit in selected cases. In our experience, the time of absorption of enteric-coated tablets is but little longer than the uncoated and therefore it scarcely seems advisable to give both at bedtime on an empty stomach. While the coated tablet will act through the night, the additional amounts of the drug in the uncoated tablet might cause side reactions or insomnia.

SUMMARY

Enteric-coated tablets of Neo-Antergan, while not acting as quickly as the uncoated, appear to achieve a smoother and longer-continued action and will give as good relief from the symptoms of hay fever and hyperesthetic rhinitis, in most cases, with fewer side reactions and in less quantity, than do uncoated tablets.

It is not maintained that two enteric-coated tablets per day is the best dosage of Neo-Antergan or any other antihistaminic. This can only be determined in each individual case with the preparation being used. In our series, two patients felt they had better relief on three tablets a day than two, although they preferred two of the enteric-coated tablets to four a day of plain Neo-Antergan.

Note: The author wishes to acknowledge with thanks the assistance of Dr. R. C. Pogge of Merck & Co., Inc. in making available supplies of Neo-Antergan tablets, enteric-coated and plain.

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BEHAVIOR OF THE NORMAL HISTAMINE OF THE RABBIT TOWARD ANTIHISTAMINIC SUBSTANCES

FRANCISCO J. FARRERONS-CO, M.D., F.A.C.A.
Barcelona, Spain

NOTWITHSTANDING all that has been published on antihistaminic agents, little is known of their course of action. From the works of Staub we know only that the antihistaminic substances 929 F and 2339 R.P. (Antergan) neither activate, combine with, nor destroy the histamine.

In order to support the latter two points of view, namely, that antihistaminic agents neither destroy nor combine with histamine, we have carried out the following experiments.

METHODS

A group of twelve rabbits, chosen only because of the considerable content of histamine in their blood, were subjected to a determination of histamine before being injected with the antihistaminic agent; blood was then extracted by intracardiac puncture, and, in some cases, by bleeding.

The blood was collected with a syringe or a heparinized vessel. The antihistaminic chosen was Antistine* (2-N-phenyl-N-benzyl-amino-methyl-imidazoline) and, in two cases, Benadryl (beta-dimethyl amino-ethyl-ben-zidryl-ether hydrochloride).

These substances were administered to the animals intraperitoneally and in quantities always greater than those marked as sufficient and efficacious in preventing lethal anaphylactic shock.^{6,9}

The determination of histamine was made according to the technique of Code, Marsoum, and Gaddum.

The results are shown in Table I.

DISCUSSION

Halpern mentions three different possible effects of the antihistaminics.

1. Diminution in the formation of histamine.
2. Acceleration in its destruction.
3. The lack of action on the receiving cells.

Other possibilities of the mechanism of action, such as the activation of the histaminase and its destruction and neutralization, have already been discarded (Staub, Chambon and Martin).

By utilizing Antistine, Staub has shown also that keeping this antihistaminic drug in contact *in vitro* with histamine for some time did not prevent activity. Later, the same author,⁹ proceeding on the fact demonstrated by himself³ that the injection of epinephrine increases the content of histamine, investigated whether this formative stimulus of epinephrine to produce histamine was neutralized or modified by the antihistaminics.

From the Section of Human Physiology of the Spanish Institute of Physiology and Biochemistry of the Superior Council of Scientific Investigations.

*Kindly supplied by CIBA, Commercial and Pharmaceutical Co., S.A., Barcelona.

ANTIHISTAMINIC SUBSTANCES—FARRERONS-CO

TABLE I. BLOOD HISTAMINE BEFORE AND AFTER ANTIHISTAMINIC AGENT

No.	Antihistaminic Quantity in Mg. per Kg. Animal Weight	Histamine in Blood per C.c.		Antihistaminic Administered
		Before	After	
1	20	0.5	0.5	Antistine
2	25	0.002	0.002	Antistine
3	30	1.25	1.25	Antistine
4	60(30-30)	1.1	1.0	Benadryl
5	60	0.96	0.6	Benadryl
6	45	1.1	1.1	Antistine
7	40	2	2	Antistine
8	45	2	2	Antistine
9	60	2	2	Antistine
10	195(75-60-60)	1.5	0.075	Antistine
11	100	1.5	1.5	Antistine
12	90	1.1	0.66	Antistine

HISTAMINEMIAS CONEJO n° 1

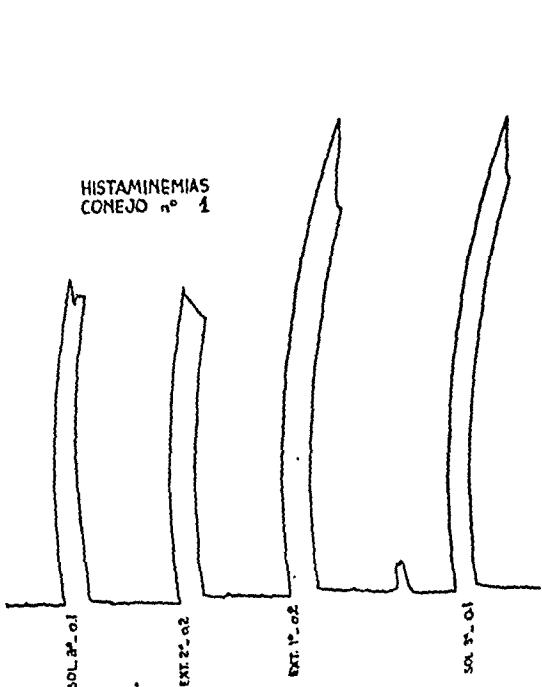


Fig. 1

HISTAMINEMIAS CONEJO n° 2

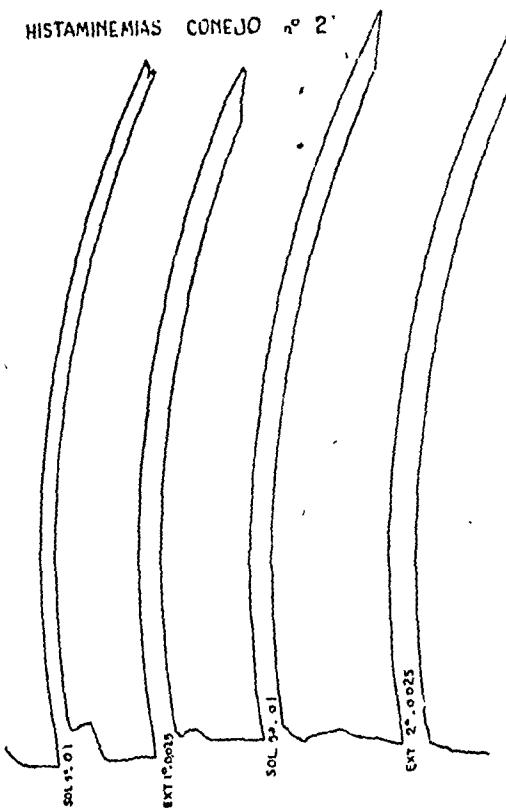


Fig. 2

His investigations confirmed the supposition that Antistine definitely acts by diminishing or annulling the hyperhistaminemia produced by the epinephrine. He concludes that the mechanism of action of antihistaminics consists in their restricting the formation or liberation of histamine.

If the mechanism of the action of the antihistaminics is not due to any inhibition of their formation, but to a displacement site of action, Staub would have found a greater quantity of histamine following injection of epinephrine, without giving rise to any abnormal phenomenon, since introduction of antihistamine would have protected the receiving cell from its toxic action. However, Staub finds that antihistaminics do act as brakes

ANTIHISTAMINIC SUBSTANCES—FARRERONS-CO

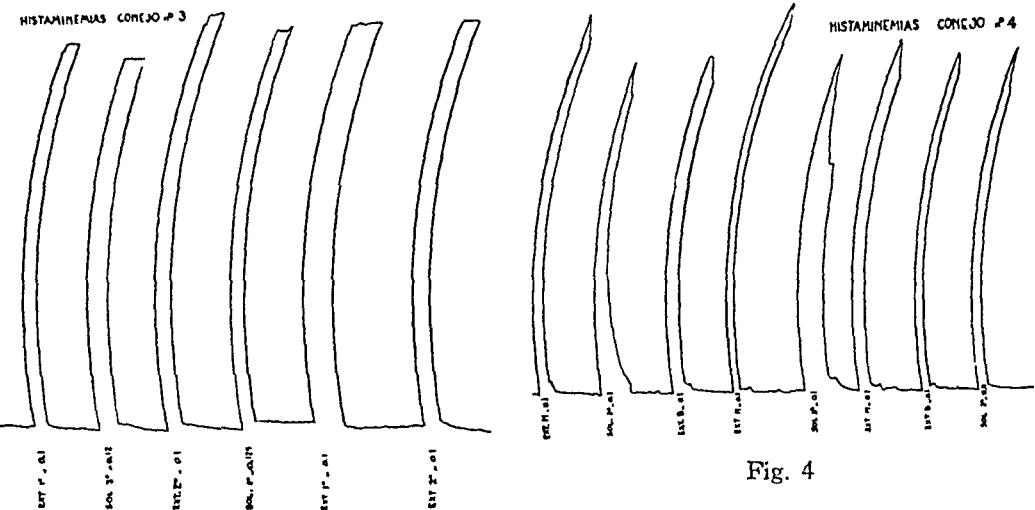


Fig. 3

Fig. 4

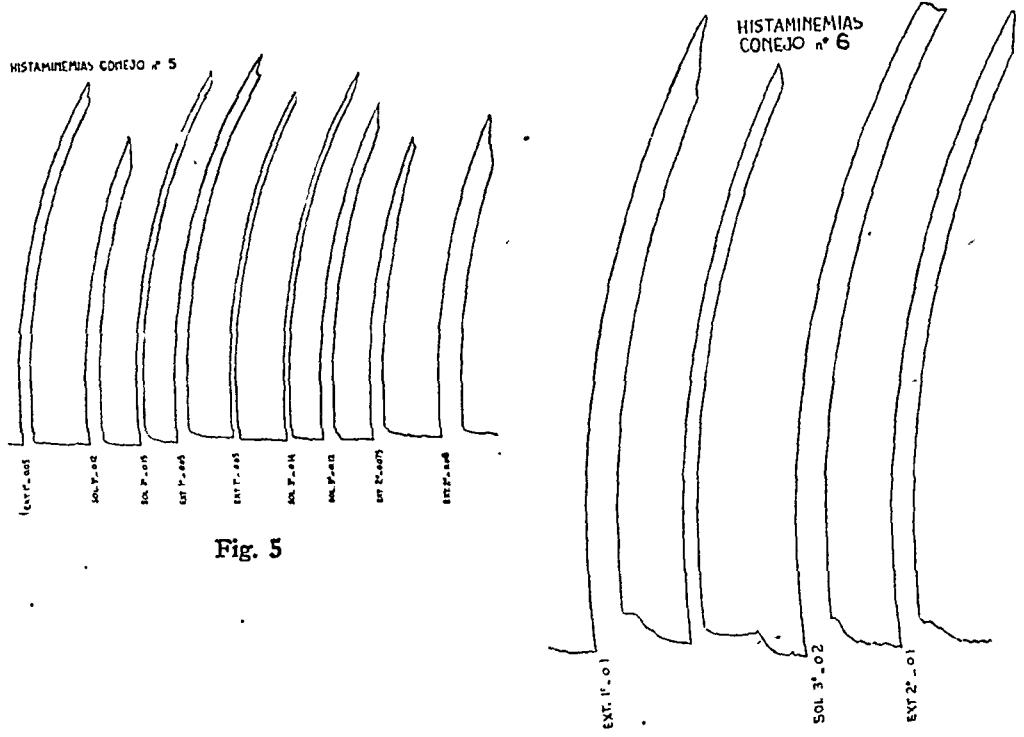


Fig. 5

Fig. 6

upon the hyperhistaminemic mechanism of epinephrine, and, therefore, he maintains that the way in which these drugs act is simply that of restricting the formation of histamine.

It is generally accepted that the mechanism of action is that the antihistaminics displace the histamine from its point of attack (Halpern). Ackermann thinks the same of arginine and like substances. Roche and Silva have the same view for histamine derivatives.

ANTIHISTAMINIC SUBSTANCES—FARRERONS-CO

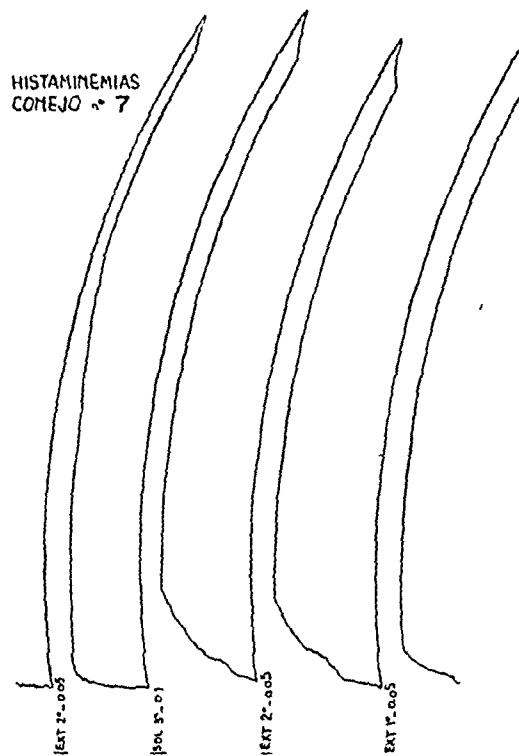


Fig. 7

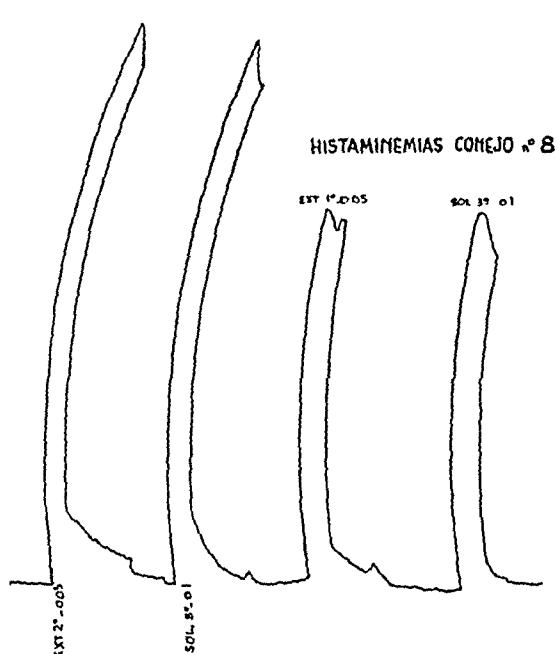


Fig. 8

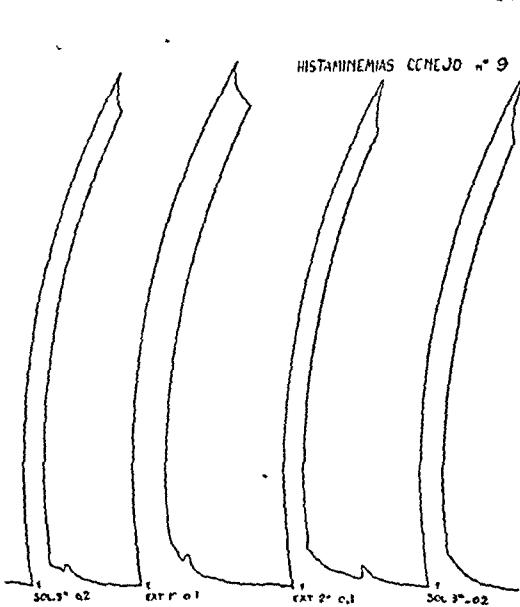


Fig. 9

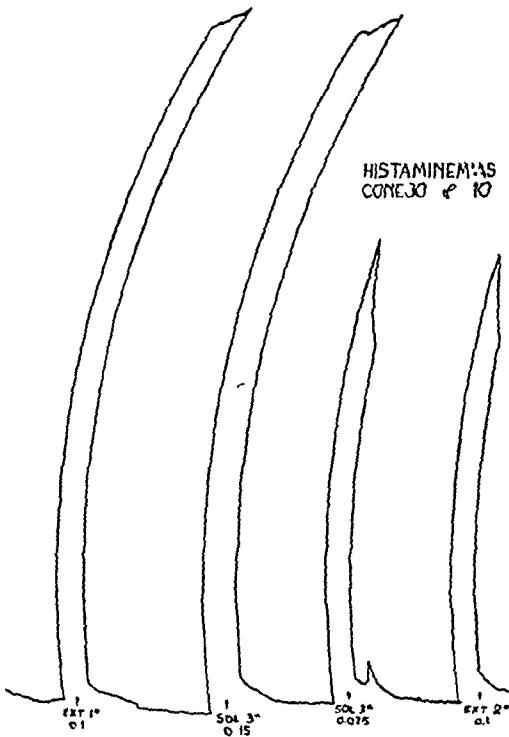


Fig. 10

Staub is of this opinion, for the 1571 F.H.; Halpern, for 2339 R.P. or Antergan; Mayer, for "Pyribenzamine"; Wells and Morris, for the benzo-hydryl-ethers; and Lehmann and Young, for anthracene-esters.

HISTAMINEMIAS CONEJO n° 11

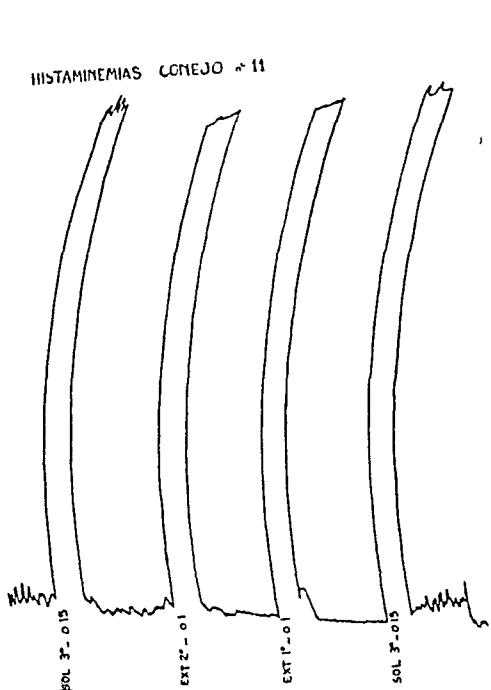


Fig. 11

HISTAMINEMIAS CONEJO n° 12

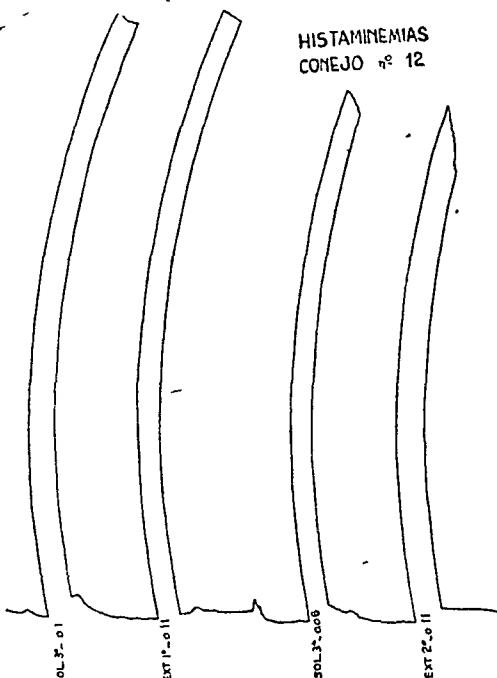


Fig. 12

We shall not discuss this as it is mentioned only as information and as our work is concerned with normal contents of histamine, where latter is already formed and of which there is no hyperfunction.

Thus it may be concluded, as other authors have shown for other antihistaminics, that those used by us also do not destroy or neutralize histamine.

SUMMARY

1. Histamine determinations have been made on twelve rabbits before and after they received heavy doses of antihistaminics.
2. With the exception of four animals, the histamine level remained invariable in all, in spite of the fact that the majority presented evident symptoms of intoxication (paresis of the lower extremities, convulsions et cetera), and some of the animals died.
3. The resistance of the physiological histamine in the presence of antihistaminics leads us to believe that the mechanism of action of these drugs is distinct from that of neutralization or destruction.

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EMOTIONAL TRAUMATA PRECEDING THE ONSET OF ALLERGIC SYMPTOMS IN A GROUP OF CHILDREN

HYMAN MILLER, M.D., F.A.C.A., and DOROTHY W. BARUCH, Ph.D.
Beverly Hills, California

IT HAS LONG been remarked by allergists and others that certain events in their patients' lives have seemed to precipitate the onset of clinical symptoms. The onset of symptoms after physical illnesses such as pneumonia, or after operations such as adeno-tonsillectomy, has been frequently noted. More recently attention has been turned to emotional as well as physical episodes.^{1,2,3,4} As a matter of fact, the question has been raised whether the so-called precipitating physical causes, such as pneumonia or adeno-tonsillectomy, may not also have carried with them an emotional etiological component.

The present paper deals with a sample of ninety allergic children with ages ranging from one year and eleven months to eighteen years (mean: 8.8). The subjects were studied both medically and psychologically. This involved the usual medical history, physical examination, skin testing and such other laboratory procedures as seemed indicated. In addition, psychological interviews were held in each case with the mother and frequently with the father. Either a diagnostic play session or an interview was held alone with the child, depending on the age.⁵

In obtaining information from parents and older children, incidents in the life of each patient preceding the first onset of allergic symptoms were investigated. The procedure was not that of immediately firing a whole series of questions. It consisted, rather, of stating that anything that had bothered the patient or his parents might be of importance, and then, as John Mitchell, for instance, has done,⁶ taking a listening and acceptant role. By this method not only was much factual information obtained, but very often, either consciously or inadvertently, episodes were related to the first onset of symptoms which had not been previously connected with it. Questions could then be used to fill in the gaps.

The traumatic episodes came to light usually in the interviews with the parents.

For example, the mother of a six-year-old asthmatic girl, at the beginning of her session with the psychologist, said that the doctor had thought the child's illness might be partly due to emotions, but she could see nothing of that sort. Sandra was a good child and well adjusted. "She never seems to get upset." She then said, apologetically, "I'm the nervous one." The psychologist reflected, "You feel your nervousness means something."

"Yes," nodded the mother. "I've been terribly upset." She went on recounting her own difficulties with the child's father. "It makes me so nervous, I don't ever feel he likes me. Once, Sandra said she didn't like me either and I got so upset.

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EMOTIONAL TRAUMATA—MILLER AND BARUCH

She was three. I remember it clearly because that was one time she did get upset. I was very hurt and cried and said I'd go away and she could get another mother. I couldn't stand talk like that. She sobbed and sobbed, not like just regular crying. She was terribly upset. I couldn't comfort her. She sobbed for hours and hours. I couldn't get her to stop. She was sick that night . . ." The mother paused, "I guess that was when the asthma started. Come to think of it, she'd never had it before."

Sometimes the traumatic episode was brought to light in the interview with the child.

Thus, an eighteen-year-old asthmatic girl who had been referred for severe and intractable eczema which had appeared for the first time in her life two weeks previously, at first declared that she could see "nothing special" to have made her break out. However, as she talked to a sympathetic listener whom she soon found did not condemn her, she brought out material that made the traumatic incident preceding the onset become clear.

Right before Christmas vacation she had been caught one night returning to boarding school with liquor on her breath. "They raised the most awful stink but *I* didn't think it was so bad."

"You're not quite sure but you're sort of proud of it," the psychologist reflected.

"But I was afraid they'd write my mother. I didn't know if they had or not and I didn't want to ask. I thought about it, though, all the way home on the train. At the station, my brother met me. He acted very mysterious. Mother was sick. I got scared.

"When I got to the house, she was in bed, all pale. She looked like death. I thought she was going to die. Then she told me she had cancer. I'd given it to her by being so bad. I didn't know whether to believe it or not; she'd always told me I'd be the death of her, when I wouldn't practice or any little thing. But anyway I felt like I was going to die . . . I couldn't sleep. I tossed and turned and began to itch. The next day I looked like sin; just as bad as I felt . . ."

With the younger children, sometimes the traumatic events came to light in the diagnostic play session and could later be confirmed by interview with the parents.

For instance, Richard, seven years old, who had had hay fever since infancy, was referred by a psychiatrist on two scores. He had been wheezing for a couple of weeks and had recently been caught choking his thirteen-months-old sister on the sly.

In his play session with a group of dolls representing his own family, he acted out a scene where he choked his baby sister. During this he said, "That's a bad thing to do. It doesn't mean he's loving her. She kicks and throws her hand over his mouth. She kicks him hard. Father and mother spank the boy and kiss the baby . . . The father says, 'Do you know how that felt?' And he starts to do the same thing to the boy. Only he choked him harder because he was bigger. Real, real hard. He fell down on the floor . . . Father said, 'I'm glad, that's taught that boy a lesson.'"

The father, at the mother's instigation, had actually choked the boy whenever he was caught choking the baby. Finally, in one of these episodes the child fell to the floor, seemingly unconscious, and the parents, overcome by guilt, stopped punishing him in this way. It was shortly after this that his wheezing began.

In his play, Richard went on to show what had happened after his father stopped choking him. Only now, the scene depicted what had occurred not in reality but in his own imagination, which to him, however, was almost as real.

EMOTIONAL TRAUMATA—MILLER AND BARUCH

"Then, everything got w-w-worse," he stammered and, then and there he started to wheeze. "Then," he went on, "they really *had* to get rid of him. They sent him out under a cobweb,—a big chokey came and chewed him up. Under the cobweb—all black—and he choked. They got all in his mouth . . ."

And a few minutes later he said eagerly, "He'd rather have daddy show him how it felt . . . Better than to throw him out and have him die."

Thus when his father stopped punishing him, Richard had taken over his own punishment. His wheezing was part of this.

From sessions such as these with both the parents and children, information on traumatic episodes apparently related to the first onset of symptoms were obtained in sixty-eight children. Separate traumatic events apparently related to the onset of separate syndromes were obtained in nine instances. Thus, although only sixty-eight individuals were represented, seventy-seven traumatic occurrences were noted preceding an initial onset for a given condition.

The largest number of traumatic episodes were seen to be related to the *loss or threatened loss of a parent*. This included the death of a parent, actual separation or desertion or what seemed to the child to threaten death, separation or desertion. In twenty-two cases episodes preceding onset of a particular symptom fell into this classification.

One child's asthma appeared at the age of seven after both her parents had been simultaneously killed in an accident. Three children (at the ages of three, five and eighteen, respectively) had come upon a parent drunk and had feared the parent actually dead. In his interview twelve years later, one of these recalled with evident emotion that he had found his mother fallen against the bathtub with blood running out of a gash on her head. "I thought she'd killed herself," he said. His father's reports confirmed the event and helped to ascribe the asthmatic onset to this date.

In five instances the mother left the child to go to work. In one instance the mother suddenly, and without preparation, turned over the entire care of the child to someone else. In six cases the mother's going away—to the hospital, on vacation or on visits without adequate preparation—preceded the first exacerbation, and in Sandra's case, already cited, the mother's threat of leaving was the antecedent event.

The threat of losing a parent may produce an emotional trauma in a child at an extremely early age. This is strikingly brought out in the case of a boy who, when seen at the age of five, was covered from head to foot with severe eczema. His mother related that the eczema began at eight months when she had left him to visit her husband who was then in the service in a distant city. That the event had made a deep impression was evidenced by the fact that the infant for months afterward would cry inconsolably whenever he saw a suitcase. At five years, the mother left the child again to go to work. At this time he had his first asthma attack.

There were three cases followed by onset where the parents left a child abruptly in school or hospital without preparation or where they told him

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that they would send him away to school. Similarly, onset of symptoms followed (in two cases) when a child was locked alone in a room for an extended period, unheeded, and crying for his mother in vain.

From the records it appeared that to these children such occurrences stood as a kind of desertion. They felt that their mother had left them and often in their minds attributed this, bleakly, to having been somehow themselves to blame.

Death in the family, other than that of a parent, preceded onset in three cases.

However, the second largest class of incidents preceding the onset of allergic symptoms had to do with marital conflict. This does not refer to the long-term continuous conflict but to sudden eruptive episodes.

In one case, for instance, such an eruptive episode in marital conflict preceded the onset when a five-year-old girl saw her drunken father beat and threaten to kill her mother. It is interesting to note that still at eleven, her attacks recurred whenever the divorced father appeared on the scene.

In ten instances the emotional upset of the mother at the sudden discovery of the father's infidelity was followed by the appearance of clinical symptoms in the child. In two cases, the father's return from the service precipitated emotional upsets in the mother by the unwelcome resumption of marital relations, and in a third, by the necessity of giving up an affair. Family peace was disrupted (also in two cases) by sudden trouble in the father's business. In another case the child heard the mother's vituperative, screaming attack on the father, charging him with not caring about his children enough to support them. In another case the onset of symptoms followed the mother's decision to get a divorce; in another they followed the mother's foreswearing sexual contact on religious grounds; in still another they followed the civil war between father and mother which arose when the grandparents moved into their home.

With four children, the witnessing of intercourse preceded the onset of the first allergic symptoms.

To give an example, David, four years old, shortly after being moved into his parents' bedroom began screaming in his first attack of asthma. "The wolf," he cried, "the wolf is going to get me." In his play session he put the dolls representing the father and mother in bed together and the little boy doll representing himself in a bed close by. Then he placed the father on top of the mother and started to sob. "Had bad dream! Big bad wolf!" The therapist reflected, "The big, bad wolf scared him." "Yes," he nodded, and pointing to the father doll, he said, "There he is. Right there!" . . . David then took a toy gun and saying that he was shooting the big, bad wolf, he had the boy doll shoot the father. He then said, "I'm a naughty, naughty boy!" and shot himself.

Still another child, a boy, eight, recounted, "I wasn't too afraid; I was afraid though. They were bumping in the air, kind of. They were rumbling around. My dad was snorting, kind of. He looked like two big eyes—a devil. I guess I was real scared!"

To cite another example, Larry, aged eight, an obese boy whose asthma had

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begun some months before, took the mother doll in his play session, put her in bed and pulled her skirts up. He then pulled the father doll's trousers down and placed him on top of the mother doll. "One day I saw them," he said. "This is what they were doing. I thought they were fighting." Then, getting confused and anxious, he hung his head and began evading, "I saw . . . I didn't see . . . They saw me . . . They didn't!" And right in the play session, he started to cough and wheeze.

When checked, his parents admitted that he had come upon them and that his asthma had begun that night.

In seven children, the first onset of the allergic syndrome occurred after the birth of a sibling. In some of these children there were tentative protests about the newcomer. Said one, timidly, "Send him back to the hospital." Said his mother, "But, he's nice. He's your dear little brother. You don't really want to give him away." Another masked her hostility cunningly under the guise of a caress. "He's so cute," she exclaimed, "I'll eat him up!" And she proceeded to bite the baby, announcing with a smile, "I just wanted to see how good he'd taste." One reverted to baby talk and began to soil and wet. On the whole, their parents reported, "They're so sweet to the baby!" In their play sessions, however, truer feelings emerged. For example, one stuck the baby's head in the toilet bowl, another poured water all over him to make him "not breathe," and another cunningly had the angels take the baby to heaven to live.

Another type of experience preceding the first onset of allergic symptoms can be classed under the heading of over-severe habit training. This sort of episode occurred prior to the first onset of a particular symptom in six cases.

To cite just one example, four-year-old Eddie's mother related that prior to the onset of his asthma several months earlier she had decided she "simply had to" break him of sucking his thumb. "I kept pulling it out of his mouth roughly," she recounted, "and I called him a sissy and told him that big boys don't do that. I showed him how it looked and finally I threatened him I wouldn't love him anymore. Then he had those awful dreams and would get me up at all hours, and the asthma began." Incidentally, he had started to suck his thumb at two years when his sister was born, and although his mother had continuously tried to stop him, the threat of not loving him was the first thing that "worked." In other cases, over-severe and punitive toilet training had similar sequelae.

Another type of episode preceding onset, seen in five cases, can be best categorized as masturbation threats.

To quote one mother of a nine-year-old asthmatic boy, "I caught Lee masturbating when he was about four and a half years old. I was very upset. The doctor said, 'Do nothing.' I couldn't stand it though. I must admit, I threatened him terribly and got furiously angry. About a year ago I told him that it would make it fall off and that he couldn't have any children if he did this. After that he got asthma, and then I told him that doing that would make him wheeze. He confessed a number of times when I asked him what he had done when he wheezed, saying, 'I tickled myself!'"

Another mother had threatened her little two-year-old girl that she would make

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TABLE I. TYPES OF TRAUMATIC EPISODES PRECEDING FIRST ONSET OF A PARTICULAR ALLERGIC SYNDROME[†]

	Cases
Loss or threatened loss of a parent.....	22
Marital conflict	20
Death in family other than that of parent.....	3
Witnessing intercourse	4
Birth of sibling.....	7
Over severe habit training.....	6
Masturbation threats	5
Physical violence or threat of violence.....	7
Surgery	3
Total	77

*French and Alexander¹ have offered a somewhat similar list of emotional factors precipitating attacks of asthma, as follow: (1) sudden intense emotion, (2) crying, (3) sexual conflict, (4) disturbance of a dependent relationship, (5) danger to near relatives, (6) identification with dyspneic attacks of others, (7) secondary utilization of attacks.

herself sore and bleeding and that the doctor would have to get a big darning needle and sew her up. Another said to her two-year-old boy, "If you get your wee hard that way, someday it will get too hard and it will break off." She took a crayon and broke it in two and said, "This way." . . . So as to make him understand.

Closely allied to this, in one instance, was another less obvious episode which apparently held the same meaning to the child. The child had been masturbating and had been told without seeming effect that his penis would come off. Then, one day the father took an animal cracker from him and bit off its leg. The child went into a panic and began to wheeze.

In six cases, episodes of physical violence done to the child preceded the initial onset of allergic symptoms, and in a seventh case, the threat of physical injury. One very rejecting mother lashed her little girl until she was almost unconscious. Another, in a drunken rage, as the father described it, beat her two-year-old "to a pulp." Said another, apologetically, "I'm so ashamed of myself but I couldn't help it. He's so stubborn, I had to beat him until he gave in and cried."

One mother did not engage in physical violence but threatened impending bodily harm to keep her three-year-old from crossing the street. This preceded his first attack of asthma. To use her words, "I scared him witless. I told him there'd be no more John. He'd get squashed under a car."

In three cases, an operation preceded the allergic onset: one adenotonsillectomy, one plastic operation on the hand, and one almost simultaneously executed adenotonsillectomy, circumcision and eye-muscle shortening operation when the child was four. In all of these cases there was inadequate preparation and the children were separated from their mothers pre-operatively and postoperatively, being placed where the mothers were not allowed to be with them.

Table I summarizes the foregoing.

DISCUSSION

The incidents which have been related as occurring in the lives of these children are obviously not unique. Many of them occur in some form or other in the life of numbers of children without being followed by any

apparent difficulties. That severe physical illness should have followed in this group can be explained only on the basis that the seed must have fallen on fertile soil—a soil prepared both allergically and psychologically. As far as the allergic preparation is concerned, this goes back essentially to the presence of reagin. But what is the psychological factor?

As the histories of these allergic children are studied in greater detail, and as some of the children reveal themselves more deeply in therapy, the meaning of the episodes cited becomes clearer, so that their traumatic nature is better understood.

When they are seen in context, there emerges one pervasive emotional factor that is common to every type of incident preceding first onset. When one speaks of loss or threatened loss of a parent, the significance is clear. To the child, emotionally it appears that the parent doesn't love him, and in most instances, as has been seen, this means specifically the mother. When marital conflict enters, the child again essentially feels afraid of losing the mother. Death of other members in the family has been seen to generate fear of losing their mother more than anyone else. Witnessing intercourse to the child appears as an attack on the mother and once more activates his fear. Birth of a sibling not only threatens loss but is a realistic loss of part of the mother through the loss of part of the mother's time and attention and, as the child takes it, of her love. To the child, over-severe habit training is in essence as if the mother were saying, "You're not good enough," and this, in turn, is followed by a feeling of not being loved, or, in extreme cases, of being disowned. The masturbation threats mean, "She doesn't love part of me." Physical violence against the child's person bears incontrovertible evidence to the child, whereas the mother's leaving him to go alone into the frightening experience of an operation again makes him feel deserted and lost.

These threats have a particularly powerful significance to the allergic child. *They confirm his fear that his mother has never loved him too well.* Nor is this fear unfounded. For, as shown in other studies,^{5,6} even though she may not be aware of it, the mother of an allergic child is almost invariably a rejecting mother. As a result, no matter how much care and solicitousness she lavishes on him, he seems to sense her inner attitude. He then feels insecure. And so any episode that appears to him to threaten further loss of his mother may prove traumatic, whereas if he were less insecure, it might not.

Ordinarily when a child feels insecure he becomes resentful and shows it by word or behavior. But it is characteristic of the allergic child that he is unable to bring his resentment out by word or behavior. He characteristically blocks the outgoing expression of his resentment and turns it on himself.⁴ He expresses it by using his allergic constitution. His asthma, hay fever or eczema then are his way of saying, "I am angry but I don't dare tell you about it. It scares me to tell you about it. I feel too guilty

about being angry but I have to do something with my anger. I want you to continue loving me, and I'm afraid that if I let you know I'm angry at you, you won't love me at all. So, I get sick."

Usually, all this is done unconsciously.

If allergic children can be helped to get their resentful feelings out in the open, instead of blocking them, they will no longer need to use allergic symptoms so much for this purpose.

In some cases referral for psychotherapy will be indicated.

Where it is necessary to remove the child from the home, not only must the child have psychotherapy but he must also find in the home-away-from-his-home a substitute parent or parents.

In many cases the allergist himself is able to facilitate the emotional care of the patient by his own approach, especially if he has gained psychological orientation. He need not diagnose the where and why of the onset or try to solve the causes of the mother's rejection. He can take the child where he is, and by accepting and reflecting the child's feelings, he can help relieve the child's emotional block.

Thus, in the child's presence, a mother starts talking of sending him to boarding school in a better climate. The physician notices the child's bothered expression. He accepts the feelings behind it and reflects them out loud by saying, "It makes you feel sort of mean and mad when mother talks like that."

He can also accept and reflect the mother's feelings. As an example, another mother complains, "I'm all worn out, I need a vacation from him." The physician accepts both her feelings and the child's, and reflects both. He says to the mother, "Sometimes you get so tired you do want to get away from him and from everything. And you," turning to the child, "you get pretty worried and kind of mad, Sonny, when you feel that mother gets that way."

In this way the physician shows that he has understood and has not condemned either mother or child. Both can feel easier. Each can feel inside himself, "Well, I'm not as bad as I thought."

By such an approach, no matter what the onset, the allergist will have shown the patient that he understands him as a person who has emotional as well as physical problems on which he needs help.

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REMARKS ON THE THEORIES OF ANTIBODY FORMATION

ADOLPH ROSTENBERG, JR., M.D., Chicago, Illinois, and MATTHEW J. BRUNNER,
M.D., F.A.C.A., Brooklyn, New York

IN THE early days of immunology it was discovered that blood from an animal which had been treated with certain microorganisms would react *in vitro* in a different fashion to the organism in question than would the blood of an untreated animal. Various types of reactions were observed, such as agglutination, precipitation, bacteriolysis, et cetera. It was hypothesized that these reactions were brought about by substances developed by the host in response to the organisms which had been introduced. To these substances the generic name of antibodies was given. The nature of these agents was unknown, and they were recognized by their biologic and serologic effects rather than by their physical or chemical properties. During the course of the years a body of knowledge was accumulated which identified the substances possessing such properties with certain serum proteins.

If blood serum is treated with chemical agents such as ammonium sulfate, certain proteins will precipitate out at particular concentrations of the salt. In accordance with these differing solubility characteristics, the proteins have been designated albumin, globulin, pseudoglobulin, euglobulin, et cetera. It has been found that antibodies are largely in the pseudoglobulin and/or euglobulin fractions. More recent study of serum proteins by electrophoretic techniques has shown that the different proteins under the influence of an electrical current have varying mobilities. The protein fractions corresponding to the different mobilities have been labeled albumin, and alpha, beta and gamma globulins. In general, antibodies have been found to be associated with the gamma globulin fraction. Antibodies, then, are serum globulins, which because of an induced physicochemical modification in their structure become capable of mediating certain forms of biological and/or serological activity by which they can be recognized.

At present, the ability to recognize an antibody depends on having a test system by which some function of the antibody can be demonstrated. If a serum or tissue extract is capable of yielding reactions such as those already mentioned, of precipitation, agglutination, et cetera, it is, of course, easy to assert that antibody is present, but it is important to realize that the converse is not necessarily true. If these reactions cannot be elicited, it does not follow that antibodies are absent. It may well be that in certain conditions which are perhaps mediated by antibodies, but in which they have not been detected, the failure is due simply to the lack of an appropriate test system.

Dr. Rostenberg is from the Department of Dermatology and from the Allergy Unit, University of Illinois College of Medicine, Chicago, Illinois.

An outstanding feature of all antibodies is their specificity. In other words, an antibody is capable of reacting only with a specific substance which, with few exceptions, is that which originally called forth the antibody. Not all substances can serve as antigens (e.g., evoke antibody), and the exact physical and chemical properties necessary for antigenicity are not yet entirely clearly defined. Suffice it to say that certain molecular aggregates, primarily proteins,* when brought in contact with the body tissues have this property. Certain cells apparently have the capacity to handle foreign protein—to distinguish, as Burnet^{6,7} says, "self from not self." The presence of alien protein in the milieu of such cells may cause them to alter (adapt) certain enzyme systems in order to cope with this foreign material. To materials which can cause this enzymatic adaptation to take place we then give the name of antigens. From this point of view the antibody can be regarded as the adapted enzyme system or the new product which arises because of the changed enzyme system acting on its substrate.

As soon as the specificity of antibodies was established, a number of theories were elaborated to account for this phenomenon. Few have stood the test of time. One of the first theories was that of Buchner, who believed that the antibody incorporated antigen or a portion of the antigen into its molecule, thereby deriving its specificity. However, it seems improbable that the very large amount of antibody which can be engendered by very small amounts of antigen could come about from an incorporation of the antigen molecules among the antibody molecules. In addition, when marked antigens, that is, antigens containing a chemically easily detectable substance such as arsenic, are used, it has been found that the antibodies resulting contain no traces of arsenic.

Ehrlich's theory of antibody formation dominated immunologic thinking for many years. Ehrlich hypothesized that certain cells of the body were endowed with a wide variety of preformed "receptors," so constituted that they would specially fit and unite with a given antigen. Under an appropriate antigenic stimulus these cells would manufacture the receptors in such quantities that some would be cast off into the blood stream. These excess receptors were said to constitute circulating antibody. It is difficult to accept the idea that the body should have preformed receptors for the almost infinite variety of natural antigens which it might encounter. It might be argued that over the long phylogenetic history of the human race a sufficiently wide variety of natural antigens had been met, so that receptors for all of them had been formed during the evolutionary process. However, the body is equally capable of forming antibodies to synthetic antigens, which are not met with in nature. Consequently, it is difficult to believe that antibodies are cast off preformed receptors.

*Certain chemicals, e.g. picryl chloride, 2:4 dinitrochlorobenzene, et cetera, are antigenic when applied as such to the skin, but there is good reason to believe that the actual antigen is a conjugate of the simple chemical and a tissue protein. Certain complex polysaccharides are, however, believed to be antigenic in their own right; that is, they stimulate antibody production without first uniting with protein or without containing any protein as an impurity.

It was not until the early 1930's that the first of the modern theories of antibody formation was advanced independently by Breinl and Haurowitz,¹⁵ by Alexander,¹ and by Mudd.¹⁷ In essence the theory proposed by these men is that antigen reaches the site of globulin synthesis where it modifies globulin through a stereochemical influence on the developing protein. In a sense then it may be said that antibody is manufactured in the image of antigen and, consequently, there is a stereochemical correspondence of the one for the other. This theory has been elaborated on by Pauling.¹⁸ While this stereochemical theory adequately explains the specificity of the antibody, certain other aspects of the behavior of antibodies are difficult to reconcile with it. First, it becomes difficult to explain the persistence of sensitivities. If sensitization reactions depend on an antigen-antibody union, then the persistence of the sensitization presumably depends on the continuing presence of antibody in the host. A sensitization may, in some cases, endure many years after the last contact with the antigen, thereby indicating that the antibody has persisted in the host for that time. If, however, the formation of antibody is contingent on the presence of antigen at the site of globulin synthesis, it is necessary to hypothesize that antigen, a foreign material, has persisted as such within the tissues of the host over all these years.

Another phenomenon difficult to explain on the basis of the stereochemical theory is the anamnestic response. The anamnestic response may be described as follows: Following exposure to an antigen, antibody formation begins after a suitable incubation period, rises in titer for a short while, levels off and slowly declines, so that ultimately there is practically no detectable antibody present for the antigen in question. If at this point the animal is given a different antigenic stimulus, not only are antibodies against the new antigen engendered, but there is a re-crudescence of the antibodies for the original antigen.† How can this be explained by the stereochemical configurational hypothesis, according to which antigen must be present at the site of globulin synthesis for specific antibody to be produced? The decline of antibody must mean that antigen gradually disappeared from the tissues of the host. If this is so, how does one explain the renewed formation of antibody under the influence of the new and unrelated antigenic stimulus? If, on the other hand, the original antigen did not disappear, how is the gradual cessation of antibody formation after the original antigenic stimulus to be explained?**

The most recent theory of antibody formation is that introduced by Burnet.^{6,7} Like Breinl and Haurowitz, Burnet believes that antigen must reach site of globulin synthesis, but does not hold with the idea that the antigen molecule remains as a scaffold or framework about which anti-

[†]In the very recent literature (see E. E. Fischer et al: J. Immunology, 61:89, 1949), there seems to be doubt as to whether a heterologous antigen can evoke an anamnestic response. There is no doubt that a homologous antigen can call forth a more rapid and abundant antibody response.

^{**}Hypotheses could be constructed which would reconcile the anamnestic response with the stereochemical configurational hypothesis, but in view of their completely speculative nature, we do not feel that a recital of them would at this place be profitable.

body molecules are synthesized. His concept is that antigenic protein causes antibody production through a modifying effect on intracellular proteinases, which are responsible both for the destruction of protein and for its intracellular synthesis.

We should like to elaborate on this theory, as we believe it to be the one that most closely approximates reality. Some of the concepts on which Burnet's theory is based are relatively new and are related to recent advances in knowledge of the chemistry and reproduction of the living cell. These concepts are concerned especially with modern theories of enzymatic adaptation and of cell replication. All cells are endowed with enzyme systems, capable of causing certain biochemical changes on appropriate substances (the substrate), so that they can be utilized in metabolism. For example, the appropriate enzyme system will, say, on one hand, cause sucrose to break down into its constituent monosaccharides and, on the other, cause proteases to hydrolyze proteins. In the presence of certain substances some cells can adapt so as to utilize or act on substances which they originally were powerless to attack, by modifying their enzyme systems. This phenomenon has been studied in detail in the case of carbohydrate-splitting bacteria. Strains of *B. coli* which are at first unable to ferment lactose will develop lactose-splitting ability after a period of time in contact with this substance. There is a time lag in the ability of the cell to acquire this enzymic ability, but once the adaptation has occurred, the descendants of these cells are able to handle the new substrate on first contact with it. This means that the enzymatic adaptation has been passed along to the daughter cells or, in other words, it has been inherited. It is not known with certainty how this inheritance is achieved, but there is evidence that in the course of enzymatic adaptation cytoplasmic self-duplicating units are formed, which in cell division are distributed to daughter cells and thereby transmit the newly acquired ability from cell to cell.*

It should be pointed out that Sabin¹⁰ on the basis of her studies with a colored antigen (*R*-salt-azo-benzidine-azo-egg albumin) has also come to the conclusion that antibody formation is related to cytoplasmic alterations in the macrophages. Quoting from Sabin:

"The hypothesis which may be formulated from these observations is that the cells of the reticuloendothelial system take up foreign materials which may be classified into two groups, namely, antigens and non-antigens. Both kinds of material are first taken into the vacuoles of the cells, indicating that a cell guards its basic cytoplasm from the immediate entrance of foreign substances. The vacuoles are the cellular organs of digestion; the cytoplasm is the zone of syntheses. In turn, the synthesis of cytoplasm is usually from normal food substances. If the material phagocytized is an antigen, it is rendered into suitable soluble form within the vacuole and then passed into the cytoplasm itself. There its presence in some way increases the synthesis of globulin and modifies some of it into antibody globulin. Thus, an antigen may be defined as a substance which can specifically modify the synthesis of cyto-

*In this connection, it is of interest to note that Billingham and Medawar^{2,3} postulate a similar mechanism for the "infecting" of white skin by black skin in autotransplantation experiments in guinea pigs.

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plasm. This process is the evolution of a change in cytoplasm in response to environment. It may be possible that the cell which has formed a new kind of globulin and still retains it in the cytoplasm is sensitized, meaning that it would react differently from the normal cell in the presence of the original antigen."

She, as the quotations clearly indicate, envisioned an intracellular cytoplasmic alteration which yielded the antibody, yet she proffered no explanation as to how the presence of the antigenic protein achieved the alteration in globulin synthesis. Nowhere does Sabin mention the concept of enzymic adaptation.

At this point it would be natural to inquire as to the evidence which links antibody formation with enzymatic adaptation. It is freely admitted that there is no complete proof that these two phenomena are connected, yet what evidence there is, is not at variance with such a hypothesis. Before considering this evidence, it should be pointed out that all known enzymes are proteins. Fagraeus¹² found that during the course of immunization plasma cells increase at the time antibodies are being manufactured and that nucleoprotein is found in the cytoplasm of these cells. Harris and Harris¹³ observed that in lymph nodes actively engaged in the production of antibodies a wide range of lymphocytes, largely younger forms, was found to have cytoplasmic granules and that their nuclei stained with pyronine, which is used to identify ribonucleic acid. It had been previously shown by Caspersson¹⁰ and Brachet⁶ that cells which were actively forming new protein were characterized by large amounts of ribonucleic acid in their cytoplasm. Bing⁴ and others have shown that when a hyperglobulinemia exists, the number of plasma cells is increased, suggesting that the plasma cells manufactured globulin. Spiegelman and Kamen²⁰ came to the conclusion that (1) genes continually produce at different rates partial replicas of themselves which enter the cytoplasm, (2) these replicas are nucleoprotein in nature and possess to varying degrees the capacity for self-duplication, (3) their presence in the cytoplasm controls the type and amount of protein synthesis and of enzyme formation. Experiments by Cannon⁸ indicate that protein depletion brings about an impaired ability on the part of the animal to manufacture globulin and to produce antibodies in response to an antigenic stimulus. The giving of adequate supplies of protein causes the serum globulin level to rise to normal levels and restores the antibody producing capacity of the animal to the full. Similarly, experiments reported by Virtanen²¹ show that a decrease in the nitrogen content of the culture medium inhibits saccharase production by *B. coli*. For this organism saccharase is an adaptive enzyme, formed by previous contact with the corresponding carbohydrate. It would thus appear that both enzyme adaptation and antibody formation occur only under conditions of protein synthesis and at such times nucleoprotein is laid down in the cytoplasm of the cell.

The question of the site of antibody formation has long been under study. For quite some time it was realized that the reticuloendothelial

system somehow participated in antibody formation, and a considerable number of experiments were carried out in an endeavor to clarify its role in this process. Early workers tried by extirpating certain tissues to assess the role of each in antibody formation. Suffice it to say that such experiments failed, for as is now realized antibody formation is not a function localized to a certain tissue or organ. The next step was to attempt to block the reticuloendothelial system, using various techniques. The results of such experiments were on the whole conflicting. Cannon⁹ has shown that if reticulo-endothelial blockade is sufficiently complete and kept up long enough, a depression of antibody formation results, but with incomplete blockade there is either no effect on antibody formation or an apparent enhancement. Attempts have been made to determine the site of antibody formation by making extracts from different organs to determine whether antibodies could be found earlier or in larger quantities in these extracts than in the serum.

McMaster and Hudack,¹⁶ using two different bacterial suspensions as antigens, found that if one antigen was injected into one ear of the experimental animal, and the second antigen into the other ear, the highest titer of agglutinins for each organism was found in the lymph nodes which drained the ear into which that organism had been placed. The concentration of agglutinins for the corresponding antigen was least in the lymph nodes of the opposite side and the concentration in the serum stayed somewhere between the two. This result seems to indicate that the agglutinins were formed in the node draining the area into which the organisms had been injected.

Similar work has been carried on by Ehrlich, Harris¹¹ and their co-workers, showing that in rabbits after injection of antigenic material into the leg distal to the popliteal lymph node, specific antibodies were found first in the node itself or in the lymph channel leading from it. The lymph in the afferent lymph channel did not contain any antibody. It seems then reasonably clearly established that lymph nodes participate in antibody formation, although these experiments do not exclude antibody formation in other parts of the reticulo-endothelial system. As a result of her studies with a dye antigen, Sabin¹⁹ concluded that "for the experimental production of antibodies one may call into action either the tissues of the liver and spleen by employing the intravenous route of injection, or local macrophages and the endothelium and macrophages of the regional lymph nodes." It appears then that antibody manufacture is a function of cells of the reticulo-endothelial system, whether localized in a viscous as the spleen, or a lymph node, or distributed diffusely as in the true cutis. Hartley,¹⁴ for example, has shown by the production of cutaneous nodules which consisted largely of macrophages that if a virus was introduced into such a nodule, antibodies could be detected earlier in extracts from it than in serum or in extracts from any other tissue.

Since the reticulo-endothelial system is not a homogeneous system of cells, one might inquire whether all the cells or only certain of them have antibody-forming powers. Sabin's studies showed that antigenic material is engulfed by macrophages and by neutrophilic leukocytes, and the appearance of antibodies in the serum coincided with the disappearance of dye protein in macrophages and with partial shedding of the surface films of these cells, indicating that these are concerned in antibody formation. The histochemical studies by Harris and Harris of lymph nodes actively engaged in producing antibodies have already been alluded to. These investigators point out that the only cell types in which there was evidence of new protein formation was in young lymphocytes and in transitional forms between reticulum cells and lymphocytes, but in no other cell types. They specifically state that no plasma cells were seen in the greatly enlarged cortex of the stimulated nodes, and the few plasma cells seen in the medullas were similar in number and location in both the control and the stimulated nodes.

Recent work by Scandinavian workers led them to the belief that plasma cells are the cells which actually elaborate antibodies. On the basis of extensive studies Fagraeus¹² came to the following conclusions: (1) repeated injections of antigen (ovalbumin) yield an evident plasma cell reaction, (2) the plasma cells do not increase after injections of non-antigenic substances or after passive immunization, (3) a clear correlation can be made between the appearance of plasma cells and antibody titers. She goes on to say, "the particular type of cells that have been interpreted here as immature forms of plasma cells in earlier investigations have been given various names, such as lymphoblasts, large basophilic cells, monocytic cells and so on. The present author has preferred to call these reticulo-endothelial elements immature plasma cells, in view of the fact that most of them, with the immunization technique that has been applied, develop into plasma cells. Some authors would, no doubt, assign them to the series of lymphocytes."

We should like to point out that it is possible to reconcile these various somewhat divergent experimental findings and weld them into one homogeneous scheme. Most authorities agree that the primitive reticulum cell or undifferentiated mesenchymal cell gives rise to a wide variety of cells, which include among others macrophages of various kinds, plasma cells, and lymphocytes. This being so, much of the argument as to the precise cell which engenders antibody is meaningless, inasmuch as all are derivatives of the same cell, and the predominating cell can vary with such secondary factors as the nature of the antigen, the route of administration, et cetera. Such a concept has even a more profound significance in light of Burnet's views. If it is hypothesized that the enzymic adaptation takes place in the primitive reticulum cell, the persistence of specific sensitization for periods considerably longer than the lives of individual lymph-

ocytes or plasma cells can be explained. If the antigen causes the enzymic alteration to take place in the primitive reticulum cell, the alteration can then be passed on to the descendants of this cell, such as lymphocytes and/or plasma cells. Assuming these cells synthesize globulin, they would now synthesize an altered globulin (the antibody) because of the inherited enzyme modification, originally induced by contact with antigen. The specificity of the antibody would be against the antigen which caused the adaptation in the enzyme system of the reticulum cell. Thus, it would not be necessary to provide evidence that the actual antibody manufacturing cells themselves came into contact with or somehow utilized the antigen. Defined according to this concept, an antigen is a substance which when picked up by the cells of the reticulo-endothelial system is capable of causing in them an enzymic adaptation, which may then be transmitted to their descendants by cytoplasmic factors. Whether the enzymic adaptation can take place in any of the cells of the system or only in certain ones is not known, but it would not be necessary that the original adaptation take place in any cell other than the primitive reticulum cell. As a consequence of this enzymic adaptation, certain metabolites of the involved cell are altered. If the metabolite is a serum globulin, then that globulin will have modifications in its structure which will enable it to yield the biologic and serologic reactions given by the substances we call antibodies.

In discussing the stereochemical configurational hypothesis we pointed out the difficulty of reconciling the persistence of sensitizations and the anamnestic response with such a theory. With the enzymic adaptation theory these difficulties are obviated. First, it becomes unnecessary to postulate that antigen persists as such at the sites of globulin synthesis for long periods of time, and one need only assume that cellular inheritance of the enzymic adaptation occurs. The evidence for this point has already been given. Second, since any stimulus which would cause proliferation of cells which altered enzymatic capacities would result in increased liberation of the specifically modified globulin, the recrudescence of antibody under a heterologous antigenic stimulus (as in the anamnestic response) is explained. The prompt and rapid formation of antibody upon renewed contact with the original antigen is even easier to explain. In this case the enzymic alteration has already been effected at the time of the original contact. It is lying dormant, so to speak, awaiting more of the appropriate substrate, and as soon as the cell encounters this it can immediately utilize it with the more or less immediate elaboration of antibody.

We regard the intracellular enzymic adaptation as the essential response to antigen; whether or not as a consequence of it a modified serum globulin is released is in a sense an antigenic accident. In the tuberculous and eczematous types of sensitization[†] no antibodies can be found in the

[†]In deference to current usage, we are referring to the tuberculous and eczematous types of sensitization as if they were distinct immunologic entities. However, it seems to us that it is likely that the eczematous sensitization is a variant of the bacterial (tuberculin) in which the full antigen is manufactured in the epidermo-cutis and, consequently, the major reactions of this sensitization are seen in that tissue.

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serum; yet certain cells (lymphocytes, macrophages) have acquired new properties towards the antigen as shown by tissue culture experiments and passive transfer experiments. We suggest that in these cells there has been an enzymic adaptation but since in this case the enzymes involved do not have to do with globulin synthesis, there is no modification in the serum globulin, and, consequently, the alteration is not detectable by means of the usual serum reactions; however, when these cells again meet the antigen, they react to it in a different fashion than does a cell with an unadapted enzyme system. Of course, it is possible that the antigens which elicit these types of sensitization actually affect different cells than do the antigens which engender the anaphylactic type of sensitization, but there is no evidence to support such a view, and there is some evidence that the same types of cells are involved. Consequently, the more likely hypothesis is that different enzyme systems can be affected according to the nature of the antigen.

Assuming this point of view to be correct, a point of nomenclature is raised. With current thinking, it is customary to refer to sessile or tissue-fixed antibodies in the tuberculin and eczematous sensitizations. To us, the specificity found in these states is contingent on the specifically sensitized cells with stereochemically (?) altered enzyme systems. An antibody is a globulin whose synthesis has been modified as a result of an enzymic adaptation. This antibody can exist freely in the tissues of the body or can be attached to certain cells. Many, if not all, antibody functions can be shown apart from the cells which elaborate them; in the case of the sensitized cells of the bacterial sensitization so far at least the manifestations of the sensitization are inherent to an intact living cell and cannot be divorced from it.

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(Continued on Page 148)

CLINICAL EVALUATION OF THENYL PYRAMINE HYDROCHLORIDE (HISTADYL) IN THE TREATMENT OF ALLERGIC SYMPTOMS

EMANUEL SCHWARTZ, M.D., F.A.C.A., LOUIS LEVIN, M.D., F.A.C.A., and
MILTON WALLMAN, M.D.

Brooklyn, New York

EVER since it was demonstrated in 1933 by Fourneau and Bovet,⁴ and in 1939 by Staub,¹⁰ that the effects of histamine in the animal body could be nullified by certain phenolic ethers, there have been a great number of similar compounds produced in our country and abroad. Because of the marked toxicity of the phenol ethers, attention was soon given to a group of related compounds in the Fourneau series with the ethylene diamine radical. From this radical were evolved the now familiar antihistaminic agents, Benadryl, Pyribenzamine, Neo-Antergan, and numerous others. Various investigators^{1,2,6,7,9} working with these drugs reported more or less similar good results for all of them. However, they all gave some degree of toxic reactions, much less than the older original compounds, but nevertheless in sufficient amount to warrant discontinuation of the drug in numerous instances. Another observation was that these drugs did not continue giving the same results all of the time. The very same patients who would obtain relief at one time would not do so at other times with the same drug, and in many instances would get relief from another type of similar drug. Also, there were many patients who would fail to obtain relief initially from one of the drugs but would not do so from another of similar nature. This led to further search for newer compounds so that more patients could be brought into the fold of those obtaining relief.

Among the newer antihistaminics that contain this ethylene diamine radical is thenylpyramine hydrochloride or Histadyl. As can be seen at a glance, it is closely related to Benadryl and Pyribenzamine.

PHARMACOLOGY

Pharmacologic investigations carried out by Feinberg and Bernstein,³ Roth, Richards, and Sheppard,⁸ and Lee and Dinwiddie⁹ indicate that thenylpyramine, or Histadyl, is generally as effective as the other well-known antihistaminics in preventing anaphylactic shock in guinea pigs treated with histamine.

CLINICAL FINDINGS

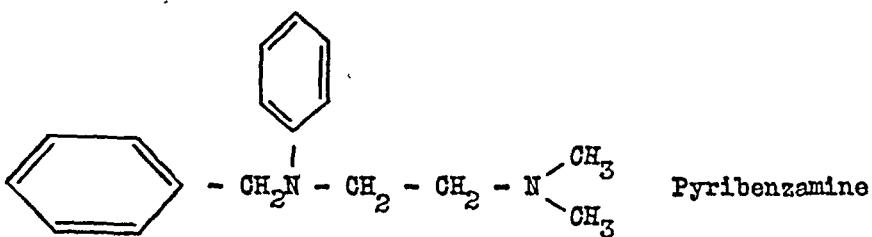
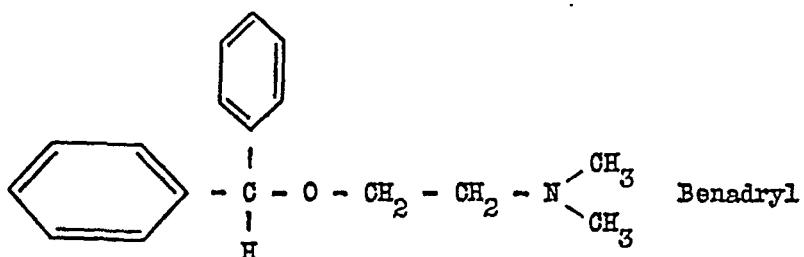
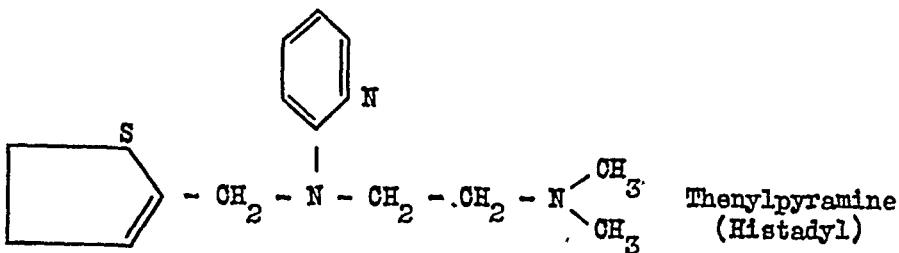
A series of eighty-nine cases were treated with Histadyl. The cases were chosen without any regard to the severity of the symptoms. All cases of hay fever, asthma and vasomotor rhinitis received routine injection treatment along with the antihistaminic. The Histadyl was given in doses of 50 mg. three times daily. In those instances where there was no relief and there were no severe toxic reactions, the dose was increased to 100 mg. three times daily.

From the Division of Allergy of the Department of Medicine of The Long Island College Hospital. Histadyl was furnished through the courtesy of Ely Lilly & Co. Dr. Milton Wallman is an Associate Fellow of The American College of Allergists.

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TABLE I. RESULTS OF TREATMENT OF PATIENTS WITH HISTADYL

Allergic Disease	Number of Cases	Relief	No Relief	Percentage Relieved
Hay fever	47	36	11	76.6
Vasomotor rhinitis	17	9	8	53.9
Bronchial asthma	13	2	11	15.4
Chronic urticaria	3	2	1	66.6
Allergic eczema	2	1	1	50.0
Acute urticaria	5	4	1	80.0
Contact dermatitis	2	1	1	50.0
Totals	89	55	34	61.8



The accompanying tables show the symptomatic results and the toxic reactions obtained in this group of patients. Table I evaluates the percentage of patients with hay fever, bronchial asthma, et cetera, who obtained relief from this drug. Relief usually occurred in one-half to one hour after ingestion of the drug, although sometimes three or four doses had to be taken before relief was obtained. As has been observed with other antihistaminics and previously mentioned, about one-third of the patients obtained relief at one period of time with the medication and no relief at another. This occurred at any time during the treatment. Relief lasted from three to six hours after a single dose of the drug. In tabulating our results, all persons who did not claim considerable relief were regarded as "no relief."

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TABLE II. HISTADYL (89 CASES)—SIDE REACTIONS (18 CASES—20%)

Side Reaction	No. of Cases
Drowsiness	9
Dizziness	2
Dryness of mouth	2
Nausea	3
Abdominal cramps	2
Weakness	1
Palpitation	1
Tiredness	1
Nervousness	2

Toxic reactions occurred in eighteen (20 per cent) of the eighty-nine cases. The type and frequency are listed in Table II.

DISCUSSION

Our best results were obtained with the hay fever cases (76.6 per cent relief) and with cases of vasomotor rhinitis (53.9 per cent relief). Although the results in bronchial asthma were not as good (only 15.4 per cent relief) as those observed with several other antihistaminic drugs, it would not be fair to draw any conclusions from the small number of cases (thirteen) in this listing. The same holds true for the skin conditions listed.

Toxic reactions occurred in 20 per cent of the cases. Drowsiness and gastrointestinal symptoms were the most common side effects encountered. The drowsiness was seldom severe enough for us to discontinue the drug.

In all of the cases the benefit derived from Histadyl was only temporary and ceased when the patient discontinued its use due to lack of medication or carelessness.

CONCLUSIONS

Histadyl, a synthetic antihistaminic compound, was used in the treatment of eighty-nine cases with allergic manifestations. In doses of 50 to 100 mg. it afforded relief in the majority of the seasonal and non-seasonal allergic rhinitis cases. These results compared satisfactorily with the action of other antihistaminics. Side effects are less frequent than with Benadryl, but about the same as with Pyribenzamine, especially as to the leading toxic symptom, which seems to be common to most of the antihistaminics, namely, drowsiness.

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PULMONARY FIBROSIS COMPLICATING ALLERGIC ASTHMA

By GEORGE L. WALDBOTT, M.D., F.A.C.A.
Detroit, Michigan

THE following case of bronchial asthma is presented because it offers certain unusual clinical and pathological features, the most significant being the fact that a psychosomatic trauma appeared to be responsible for death.

CASE REPORT

Mr. J. L. H., forty-six years old, was seen in September, 1948. He had just returned from a four months' stay in Arizona, where he had sought relief from chronic intractable asthma with which he had been afflicted for twenty years. There was an allergic family background and a history of frequent nasal and bronchial catarrhs, of croup in early childhood, and hay fever since 1925. The asthma had been present for ten years, at first confined to the grass pollen season and since 1946 assuming a perennial and persistent course. During the past six months the patient had become greatly debilitated, spending much of his time in bed, with dyspnea on the slightest exertion and with changes of temperature. Ever since he was skin tested eight years ago, he had strenuously adhered to an elimination diet, avoiding, to the point of fear, such foods as chicken, turkey, nuts, eggs, milk. In Arizona, he experienced slight relief from May through August. Since then he had had constant dyspnea. His treatment up to this time had consisted of practically all known medications for asthma, including sulfa drugs and penicillin, with emphasis on strict elimination of offending foods, with habitual use of the epinephrine spray as well as self-administration of epinephrine injections.

On physical examination, the patient was about 15 pounds underweight; there was relatively little cyanosis. There was a peculiar type of breathing which might be described as air hunger, both inspiratory and expiratory. Except for some wheezing in the tracheo-bronchial area, very few rhonchi were heard. The lower portions of the lungs appeared to be rigid, the breath sounds being hardly audible, and there was marked hyper-resonance, which was somewhat suggestive of pneumothorax. It was noted that the wheezing ceased entirely as soon as the patient's attention was drawn away from his ailment. In spite of the history of chronic sinus catarrh, the nose and sinuses were clear on transillumination and on x-ray examination. The heart rate ranged between 90 and 120; the sounds were faint but clear. The white blood count was within normal limits, the eosinophiles ranging up to 12 per cent. The sputum was nonpurulent. A bronchogram showed emphysema, evidence of an apical pleurisy and an arrested lesion in the right apex. Lipiodol did not reach the peripheral portions of the lungs (Fig. 1). A therapeutic bronchoscopic lavage ten days later (Dr. J. Birch), indicated that this was due to marked spasm in the secondary bronchi; there was practically no mucus in the bronchi. There were otherwise no noteworthy findings.

Intradermal skin tests revealed numerous 1 to 3- plus reactions to all types of antigens. The following inhalants were considered clinically significant and selected for hyposensitization: short and long ragweed, English plantain, timothy, June grass, Monilia, smut, Hormodendrum and Endo house dust. In addition he was given hyposensitizing injections for milk and egg.

After futile attempts at relieving the patient at the office, he was hospitalized on September 13. He was given a 2800 calorie diet, disregarding all food sensitivity,

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four daily injections of the above named pollen and inhalants in gradually increasing doses, and three blood transfusions. On this regime the patient improved steadily. It was possible to discontinue all symptomatic medication. He was ready to be discharged

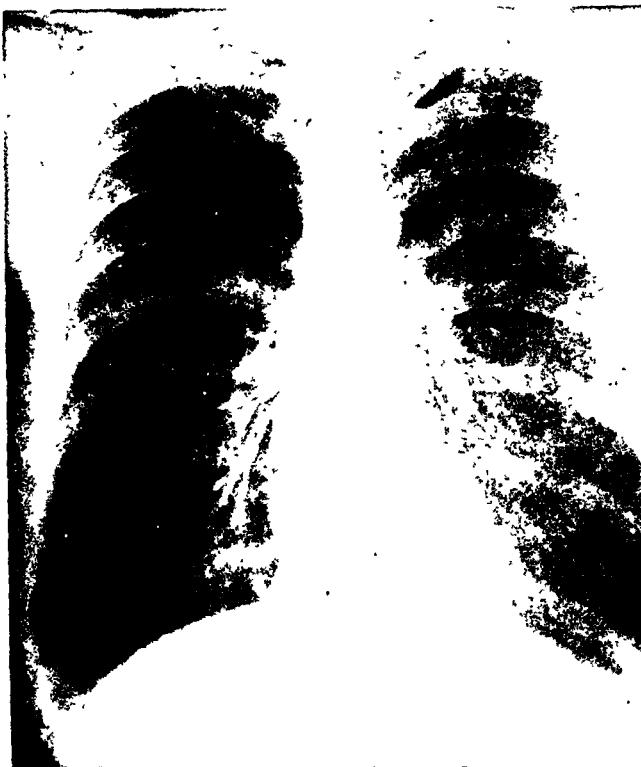


Fig. 1. Bronchogram showing obstruction of bronchi in lower portions of lungs. Bronchoscopy revealed marked spasm in the obstructed areas and no mucous plugs.

on the fifth hospital day. At the instant when his wife entered the hospital room to take him home, he developed severe dyspnea, resulting in an asthmatic attack which lasted for two hours.

Because of this and other psychosomatic features, it was attempted to obtain further data on his background. The patient had lost his father at the age of eight and had to work hard ever since in order to secure a livelihood for himself and his mother. He had seen two members of his family die from asthma and had always been told by doctors as well as by his family that asthma is incurable. He suspected his heart to be failing because a doctor once told him that he had low blood pressure. The fact that several electrocardiograms had been entirely normal failed to allay his worry on this score. Most therapeutic measures which he had tried relieved him at first for a few days only and then lost their beneficial effect. His wife treated him as an invalid, waiting on him on every occasion. She had to dress and undress him daily, a procedure which took at least forty-five minutes. He greatly resented her insistence on assisting and babying him, a fact which led to daily arguments with her. His wife's family had objected to their marriage on religious grounds. He frequently indicated that he "hated" his son. He felt very insecure in his job. While being well-liked by his fellow workers and superiors, he was in constant fear that he would lose his job and thereby his only chance of making a living. Nevertheless, his employer was personally interested in him, to the extent of paying his medical expenses.

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for over a year and a half. At no time within the past ten years had he gone to bed without taking some medication, usually large doses of epinephrine and barbiturates. Yet, he never slept more than one or two hours at night, and had to catch up on his sleep during the morning and noon hours. The noise made by the children of his upstairs' neighbor interfered with this routine and constituted a source of annoyance to him.

Much time was spent in convincing him that only very few patients die from asthma and that his case was curable. His wife was advised that her excessive attention was harmful to him. With the aid of placebos, we succeeded in eliminating sedatives and epinephrine. He was soon able to dress himself and managed to take daily walks outdoors and other light exercise. His asthma improved to such an extent that the minor attacks following exertion began to subside. He made daily visits to his office in the morning, spending the afternoons at the clinic where he was given hyposensitization treatment and where his problems were discussed with him. There was a gain in weight of 5 pounds. Two minor set-backs in late October, probably due to upper respiratory infections, responded well to treatment with penicillin.

About the early part of November, eight weeks after he was first seen, for some unknown reason, the attacks became more severe. After the usual symptomatic therapy had failed, he was referred to a psychiatrist (Dr. L. C. Foster) who brought out the following additional facts: There had been an extreme hostility of the patient's mother towards him practically throughout his whole life. When he was born, she expected a girl instead of a boy and she seemed to hold this mistake of Nature against him throughout his life. She did not wish him to marry and did not wish him to have children. Whenever he spoke about his mother he became flushed, excited, threw back his head and started his labored breathing. The psychiatrist considered his wife's overprotective and maternal role towards her husband another major issue. It made the patient assume the attitude of invalidism very early in his illness. The patient was very eager to discuss his affairs and wished to "evacuate" all his problems to the psychiatrist.

After the first appointment there was immediate improvement in the patient's general condition. About November 18 he again developed an upper respiratory infection associated with slight fever, marked wheezing, expectoration of purulent sputum, and a leukocytosis of 23,000. There was some edema in his ankles. The pulse rate ranged between 110 and 120. He was again given procaine penicillin in daily doses of 300,000 units for ten days. The fever and general malaise subsided but the asthma was very difficult to control. He resumed some of his previous medications, including the epinephrine spray. On November 29 a short interview with the psychiatrist benefited him materially. The following day he was to be seen again by the psychiatrist, but after waiting in my office for several hours he was told the appointment for this day had to be cancelled. I, therefore, attempted to reassure him and to relieve his tension, promising him that he would be seen by the psychiatrist on the following day.

On the morning of December 1, he was given an injection of 300,000 units of penicillin, and two hours later an intravenous injection of one-third of the $3\frac{3}{4}$ grain ampoule of aminophylline. His general condition seemed satisfactory. Having again failed to meet with the psychiatrist at the appointed hour in the morning, he continued to wait for him in my office. At 3:00 p.m. I was notified that through some misunderstanding the psychiatrist once more had to postpone the appointment. When the patient was given this message, he instantly became pale, broke out in cold perspiration and developed general collapse. His pulse rate rose to 220, the systolic blood pressure dropped to 65 over 30. He began to gasp for breath. Two c.c. of caffeine sodium benzoate failed to improve him. As his condition gradually deteriorated, he was hospitalized. The admitting house officer gave him 1.0 c.c. of Digalen intravenously, $3\frac{3}{4}$ grain of aminophylline, and 1/10 c.c. of epinephrine. The cardiologist's

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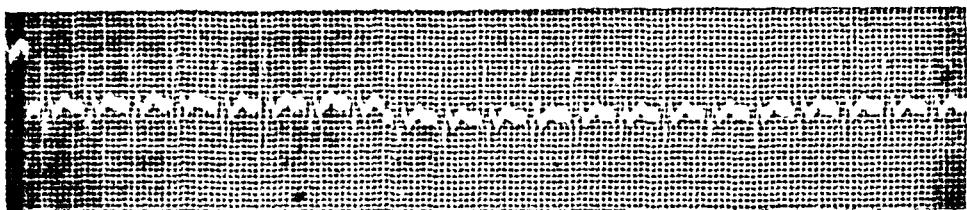


Fig. 2. Electrocardiogram showing supraventricular tachycardia probably of nodal origin. (Only one lead was taken because of technical difficulties.)



Fig. 3. Microscopic sections of lower lungs showing marked interstitial fibrosis (a) and peribronchial inflammation (b) and ruptured alveoli.

examination (Dr. W. Cooksey) revealed a moderate degree of dyspnea but very little cyanosis. There were no râles and no rhonchi. The heart sounds were faint but clear. His diagnosis was acute paroxysmal tachycardia. The electrocardiogram (Fig. 2) at this time tended to confirm this diagnosis. There was no response of the pulse rate to carotid pressure. The patient was given 3 grains of quinidine, and the orders for further doses of epinephrine and digitalis were discontinued. The patient gradually deteriorated and expired at 9:00 p.m. As cause of death, the cardiologist considered "myocardial exhaustion" and felt that ventricular fibrillation, possibly aggravated by the single dose of epinephrine and the intravenous digitalis might have been a terminal feature.

The autopsy showed no pathologic lesion in the upper lobes of the lungs other than emphysema. In the lower portions there were several emphysematous blebs. There was no mucus in the trachea or the bronchial tubes and no inflammation of the bronchial mucosa. The heart was entirely normal in size and appearance, the liver slightly enlarged. There was some ankle edema and some passive congestion in the kidneys, liver and spleen.

Microscopically the upper lobes of the lungs appeared normal. The sections from the lower lobes (Fig. 3) exhibited marked interstitial fibrosis, some hypertrophy of the bronchial walls and peribronchial inflammation. The pathologist believed that death was due to paroxysmal tachycardia and that the fibrosis in the lungs represented a complication of allergic asthma but had no bearing on the cause of death.

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DISCUSSION

The allergic history, the positive response to skin testing, and the eosinophilia definitely establish the primary diagnosis of allergic bronchial asthma. However, at autopsy the cardinal findings of asthmatic death, namely, the presence of thick tenacious mucus in the bronchi, were lacking. There was thickening of the bronchial musculature as well as some foci of leukocytosis and eosinophilia. The thickening of the bronchial musculature might have resulted from persistent spasm which may or may not have been aggravated by his psychosomatic state. The peculiar type of breathing and complete lack of aeration in the lower portions of the lungs noted on auscultation and suggested by the bronchogram was explained at autopsy by the uniform fibrosis of large portions of pulmonary areas in the lung bases which were evidently completely eliminated from respiratory function. Such fibrosis which resulted in formation of ruptured alveolar blebs has not been stressed as a major finding in allergic asthma.

The most striking feature was the mode of death. The patient had not been in a critical condition until the psychic trauma occurred, namely, the disappointment of not being seen by the psychiatrist. This did not, as to be expected, elicit an asthmatic seizure but a true case of paroxysmal tachycardia corroborated by electrocardiographic evidence. Practically no wheezing was present when the patient was lying flat in bed. There was no indication of anaphylactic shock, such as pulmonary edema and petechial hemorrhages of the lungs and other organs, nor was there evidence of cardiac damage at autopsy. It is well known that death may be precipitated by a psychic stimulus and that the autopsy in such instances does not give any clue whatsoever of the immediate cause of death. In our case there was clinical and pathological evidence of a major inhibition in respiratory function which may have been sufficient to account for death.

SUMMARY

A patient with chronic allergic asthma susceptible to marked psychosomatic aggravation contracted the clinical syndrome of paroxysmal tachycardia following a psychic trauma. This was associated with severe shock and followed by death. The autopsy failed to establish the cause of death, the heart being of normal appearance and the characteristic findings of allergic asthma being absent. Instead, the lower portions of the lungs exhibited fibrosis and ruptured alveolar blebs.

10 Peterboro

DISCUSSION

MILTON M. HARTMAN, M.D., San Francisco: I believe that the title of "An Unusual Case of Asthma with Fatal Termination" would be a more accurate designation for the excellent case description that Dr. Waldbott has just presented. There appears to have been ample organic cause for exitus without bringing in a psychosomatic factor. The emotional state certainly can modify or aggravate the physical reactions of an individual with the allergic constitution, but only if serious organic damage is present can the balance be tipped in favor of the Grim Reaper. The basic reflexes in

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the unconscious stratum are directed toward self-preservation, and in a showdown outweigh any immediate tendencies toward self-destruction resulting from conflicts in the subconscious. Even conscious desires for self-destruction are nullified except in the presence of a definite psychosis. Few who have committed suicide could be considered sane.

The current fashionable swing of the medical pendulum to psychosomatic medicine has unfortunately resulted in labeling any disorder for which no immediately obvious inflammatory, neoplastic, metabolic or traumatic cause can be found as "psychosomatic." This is most unfair to allergic disorders, for their causes are only infrequently obvious, and painstaking investigation is usually required.

Death from bronchial asthma uncomplicated by pre-existing renal, heart, or suppurative lung disease should be a rarity. When it does occur there must be a definite anatomic or physiologic cause. The discussor's investigation of deaths from "uncomplicated" asthma in the San Francisco Bay region (1943-1948) which led to his studies on water and electrolyte disturbances during status asthmaticus revealed the following causes of death:

Acute myocardial infarction.....	3 cases
Spontaneous pneumothorax.....	1 case
Morphine administration.....	7 cases
Bronchial and bronchiolar obstruction from mucous plugs...	4 cases
Dehydration	5 cases
Hypopotassinemia (consequence of improper hydration following starvation and dehydration).....	6 cases
<hr/>	
Total	26 cases

Needless to say, access to many case records was impossible to obtain. Note that the deaths in only the first two categories were unpreventable. More publicity regarding the effect of morphine upon asthmatics will eventually end that menace. Deaths in the last three categories are preventable by bronchoscopy with aspiration, adequate prophylactic hydration, and by corrective hydration under laboratory control. I may add that three of the deaths due to respiratory muscle paralysis from low plasma potassium had been considered "psychosomatic." To one familiar with the clinical course and electrocardiographic changes of such cases, the reason for exitus was obvious from the case histories.

COTTONSEED PROTEIN VS. COTTONSEED OIL SENSITIVITY

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study of food allergy may be adopted by others in order that our knowledge of this disorder may be enhanced.

The author wishes to acknowledge with thanks the technical help of Misses Gloria Seeberg and Cecilia Spearing.

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EPINEPHRINE IN THE TREATMENT OF MIGRAINE

PERRY A. SPERBER, M.D., F.A.C.A.

Providence, Rhode Island

THE ETIOLOGY of migraine has not been definitely settled. The most acceptable theories of this syndrome consider the factors of heredity, allergy, and endocrine disorders. A realization of the personality types involved and their reactions to the stresses and strains of life is important.

Most authorities believe that the essential pathologic physiology consists of a period of cerebral vasoconstriction followed by vasodilation. The headache is thought to be due to the latter. Ergotamine tartrate is probably the most useful drug in the treatment of migraine. It is believed to act by constricting cranial arteries. The unpleasant side effects of the drug are supposed to be reduced by the new derivative dihydroergotamine.

It is the purpose of this paper to present the results attained with the use of epinephrine and to gauge its effectiveness as compared with ergotamine.

A severe case of migraine which had never responded to any type of medication previously used prompted this investigation. The patient felt "her head was going to explode" from internal pressure and she begged for relief. Her symptoms were thought to be due to extreme vasodilation. Cautiously a small dose of epinephrine was given to observe its effect and see if we could secure vasoconstriction. The dose was .012 c.c. or 1/80 c.c. of 1:1000 aqueous solution given subcutaneously. Almost complete relief followed within five minutes. A second injection of the same dosage cleared the headache.

About one month later the patient returned with a new attack. She again quickly responded to the drug. It was suggested that she try ephedrine orally the next time she had migraine. Upon her following visit she stated that the latter medication had very little value and she wanted Adrenalin.

This patient was a thirty-year-old married woman with domestic, marital, and family difficulties. There was no allergic history nor was there any correlation between foods and the attacks. Migraine had been present for about ten years. It started with a unilateral headache which soon became generalized. There were visual disturbances, nausea, and emesis. No method of therapy previously used had any effect on the syndrome. The patient would recover after two or three days. Demerol or morphine would give temporary relief from the headache, but the migraine would run its usual course. Epinephrine on three successive occasions stopped her attacks. The first one was about twenty-four hours' duration, the others were about six hours in length.

The second patient was a forty-five-year-old married woman who was working as a domestic to support her husband and son. She was intelligent and formerly was a typist but was now unable to compete with younger workers. She disliked her job. Her family was a distinct problem. Migraine was brought on by emotional conflicts, family quarrels. In addition, chocolate, peanuts, and cheese initiated headaches.

The patient was observed in about ten different episodes. They varied from about one-half hour to twenty-four hours in length. If used early in her attacks, ergotamine either orally or subcutaneously in 5 to 10 mg. dosage

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gave relief. The same was true of epinephrine in 0.25 c.c. injections. With either drug the migraine was helped for about one-half to one and one-half hours. If the attack was mild, it would soon terminate; if severe, it would require re-administration of the particular medication used. Sometimes, if too severe, neither drug would help. If seen late, neither had any effect. However, while the two drugs appeared to be equally effective to me, the patient thought ergotamine gave more prolonged relief, although it made her sick.

Headache started with pain in the left eye and then involved the entire head. Attacks varied from mild to very severe. The usual drugs were ineffective, as were the so-called antihistaminics. Epinephrine and ergotamine both helped. Ephedrine orally was useless.

The third case was that of a forty-two-year-old man. Migraine was present for about twenty years. He had a very nerve-racking job which upset him a great deal. He was also allergic to chocolate, anything containing vitamin B in the form of medication, and liver injections. These initiated migraine as well as nervous tension. The ordinary drugs gave no relief. Demerol, codeine and morphine by hypodermic administration gave temporary help until they wore off. They did not stop an attack. Ergotamine was ineffective orally or subcutaneously. Mild amelioration of the syndrome could be effected by epinephrine for short periods of one-half to one and one-half hours. It aborted light attacks. Doses of .05 c.c. were used.

Attacks started with pain over the right eye and then spread to the right posterior head and neck. In severe headaches the whole head became involved. Dizziness, nausea, vomiting, and visual disturbances ensued. The patient was seen in about twenty attacks of migraine. In severe ones neither epinephrine nor any other drugs were effective.

The fourth case was that of a twenty-eight-year-old man. He had migraine for about eight years. Nervous tension or sudden extremes of temperature would bring on an attack. This was characterized by hemicranial headache. At first these responded to aspirin and related compounds. Later they became more resistant, and sedatives were needed. Ergotamine was of no avail. Epinephrine in doses of .05 c.c., repeated if necessary, would stop an attack. He was seen twice.

The fifth patient was a small, highly neurotic woman of fifty-two years of age. Her condition was complicated by asthma and a multiplicity of food allergies. Economic pressure was severe. Migraine dated from the loss of her husband five years ago. Headaches were right-sided, being confined to the right temporal and occipital areas. Visual, equilibrium, and gastro-intestinal symptoms were present. Epinephrine in doses of .025 and .05 c.c. and ergotamine both alleviated the syndrome. The former was preferred because there were no side effects. The patient was seen twice.

The sixth patient was a twenty-five-year-old girl with a history of migraine of two years' duration. The patient had an explosive personality and a migraine which could be elicited by tension or eating of chocolate. Both ergotamine and epinephrine in small doses of 0.25 c.c. would stop the attacks. The headaches were moderately severe. She preferred ergotamine as she said the effects seemed to last longer. The patient was treated on three occasions.

The seventh case was that of a thirty-five-year-old woman who had the syndrome for seven years. She had a left hemicranial involvement. There was no history of allergy. She was seen only once. She had used ergotamine, which gave her the usual side effects. After being relieved by epinephrine in a dose of .05 c.c., she stated that she preferred this drug to ergotamine because she had no side effects from it.

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DERMATOLOGIC ALLERGY

RUDOLF L. BAER, M.D., F.A.C.A., New York, New York
MORRIS LEIDER, M.D., F.A.C.A., Brooklyn, New York

In resuming authorship of the progress notes on dermatologic allergy, the present writers refer the reader to the excellent review by Epstein and Macaulay²⁴ on the more recent publications on dermatologic allergy and also to their own previous review⁷ where an extended discussion was given on the general theory of allergy. In the previous review it will be found stated that adherence to the precepts of von Pirquet,⁹⁷ Schick and Sulzberger⁸⁹ still forms the most secure foundations for the concept of allergy. The newer knowledge of immunology, serology, biochemistry and biophysics of antigens, antibodies and antigen-antibody interaction has served to point up the sturdiness of the foundations laid down by them. The heuristic value of the original concept of allergy as acquired, specifically altered reactivity in the direction of either increased or decreased sensitivity is what made so many recent advances possible. Consequently, one must deprecate the latter-day looseness of equating allergy only with clinical hypersensitivity and dissociation of acquired immunity from it or of talking of allergy as something that always is based on a histamine mechanism. In fact, a good case can be made out to prove that all allergic transformations are beneficial *in intent*; and even if some allergic changes are harmful *in effect*, many more are life saving.

ON THE USE OF CERTAIN WORDS, TERMS AND PHRASES IN THE FIELD OF ALLERGY

One often reads articles or hears technical conversation in which a patient is referred to as "an allergic" or statements are made to the effect that "there is (or there is no . . .) past history of allergy" or "there is (or there is no . . .) history of allergy in the family." It would seem that the implications attaching to allergy from the above contexts are misleading. For one thing, it is suggested that allergic transformations are somehow always pathologic and harmful and that a person who acquires, or who is capable of developing, an allergic state is inherently a special sort of person, quite different from ordinary mortals in health or disease. In reality, the skin is an excellent indicator of the fact that no one can exist long in this world without quickly developing allergic states or responses to many things. For example, nearly everyone who gets vaccinated against smallpox or immunized against diphtheria and tetanus or injected with pertussis, influenza, cholera, yellow fever vaccine, et cetera, becomes allergized. Even without these artificial events, from the moment of birth, perhaps even in gestation, specifically acquired altered reactivities begin to develop against foods, microorganisms, inhalants, contactants, drugs, et cetera. So everybody has a past history or background of allergy in himself and family, and that makes everybody "an allergic."

This semantic confusion arises because so many of the clinical problems in the general field of allergy are of the category that has been aptly designated as *atopy*. Now, it is all right to refer to a human being as an atopic or to state that there is (or there is no . . .) history or background or family history of *atopy*. The atopic is indeed a bit of a person apart. About 10 to 30 per cent of the population is said to be of the atopic habitus and thus candidates for diseases associated with the atopic tendency. The other 70 to 90 per cent are apparently incapable of spontaneously developing atopic disabilities nor can the majority of the atopic states be induced in them artificially. All persons, however—atopics and non-atopics—are

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capable of acquiring, in the course of natural events or by experimental means, any of the *other* varieties of allergic transformations, e.g., eczematous sensitizations, tuberculin-type sensitizations, drug sensitizations and eruptions and immunities based on stoichiometric neutralization of toxic antigens by specifically developed neutralizing antibodies.

Another rather objectionable use of the word "allergic" is when it is employed as an adjective to modify a material as in "non-allergic covering" or "hypoallergic nail polish." Obviously the word "allergenic" is intended. All of this may seem to be carping objection, but we find that the lay public as well as even some of the general medical public is confused by this misuse of words.

ALLERGIC ECZEMATOUS CONTACT-TYPE DERMATITIS

Eczematous sensitization is still a major dermatologic problem. Considerable strides have been made during the past years in elucidating the manner of induction and maintenance of this allergic state, the mediation of it by allergens and antibodies, the modification of it by hyposensitizing procedures and through "spontaneous" loss of sensitivity.

In the diagnosis and management of allergic eczematous contact-type dermatitis, it would not have occurred to most workers in this field that the patch test properly applied and interpreted is not of indubitable value. But it is Sutton's⁹¹ thesis that the patch test is overrated and largely needless, as he finds it adequate in cases clinically diagnosed as dermatitis venenata to institute a rigid local quarantine of the affected area, permitting nothing but the patient's hands, water, air, petrolatum, cellulose and selected cotton coverings to approach it until improved (an optimistic two weeks) and then to practice gradual re-exposure to various contactants until the allergen culprit reveals itself by a clinical recurrence or exacerbation. This advocacy of a routine of elimination and re-exposure would have been a progressive recommendation about thirty years ago, before the easy, much more harmless and frequently definitive patch test routine was perfected. But as of modern times, it is a backward step to suggest that finding the specific cause in cases of eczematous sensitization is academic perfectionism. Suppose, for example, that it is found in a particular case that an eruption arises from the wearing of a particular fur coat or a certain pair of shoes or metal earrings. Would it be enough to say that this fur coat, that pair of shoes or these earrings are at fault and that with avoidance thereof the problem is ended? It is quite possible and even probable that it is merely the paraphenylenediamine of the rabbit dyed mink that is the allergen. Then obviously genuine mink can be worn, but all other materials containing paraphenylenediamine or treated with this material, be they hair dyes, furs, cotton or leather, are extremely likely to be harmful. In general, it should be the physician's objective to prove, if possible, the specific substance, i.e., often the simple chemical in a material, that is causative, because only then a whole class of contactants may be advised against prophylactically. Aside from the inadequacy of Sutton's routine in the practical management of allergic eczematous contact-type dermatitis, it is hard to imagine how further progress can be made in eczematous contact-type allergy by such incomplete investigation.

Complete and detailed studies have brought us newer knowledge on multiple epidermal sensitization on the basis of cross-sensitization between chemically or immunologically related substances. It has been long known that substances may be so related that while allergic sensitization may be induced by a solitary agent, the allergic state sometimes may be elicited by other compounds which are related to the original sensitizing substance. Cross-reactions between the oleoresins of ragweed and pyrethrum and between poison ivy, oak and sumac were early observations. The original work of Mayer⁵⁹ in 1928 and the recent investigations of Sidi,^{81,82} Dobkevitch,^{21,82} Meltzer,⁶² Leider,⁸ Mayers,^{60,61} and Baer^{6,8,21} on substances which

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contain an amino-group in the para position on the benzene ring bring the subject down, at least for this group of relatively simple chemicals, to more desirable levels of chemical and molecular structure, positional arrangement of radicles, et cetera. Thus Mayer's revelation of the formation of compounds of quinone structure, their allergenic activity resulting from the chemical transformation of paraphenylenediamine and the similar transformation of azodyes, and the subsequent demonstration of cross-reactions to other substances, on a chemically as yet unexplained basis by Sidi, Dobkevitch, Baer, Leider, and Meltzer, have opened up new possibilities of predicting and explaining hitherto mysterious persistence and exacerbation of eczematous episodes by overt or occult exposures to chemically or immunologically related substances.

The occurrence of an extremely wide spectrum of hypersensitivity to this group of substances in a patient with allergic eczematous dermatitis due to monoglycerol ester of para-aminobenzoic acid is described by Meltzer and Baer.⁶² The patient reacted to many sulfonamides, local anesthetics, nitro compounds, azodyes, paraphenylenediamine and aniline. Despite the extent of the sensitization, it was still considered specific for compounds which contain an amino group in the para position on the benzene ring.

Laden and Wallace⁴³ studied eight cases of contact dermatitis of the hands due to local anesthetics, an occupational dermatosis in dentists. All cases were due to procaine or closely related compounds; para-aminobenzoic acid did not produce positive tests.

The fact that not all reactions ensuing after penicillin injections are due to penicillin itself is indicated by the case of Peck and Feldman⁶⁸ of a hand eruption in a physician due to the procaine in procaine penicillin. Cross-sensitization to certain other local anesthetics, sulfonamides and nitro compounds was present as in the cases of Sidi⁵¹ and Meltzer and Baer.⁶² That the eczematous sensitization to this type of compound can be made manifest by oral administration of these compounds was demonstrated by Sidi and Dobkevitch⁸² with feeding of procaine and sulfonamides. The feeding caused eruptions, flareups of old sites of dermatitis and fever. This fits in with the results of feeding certified food azodyes in paraphenylenediamine-hypersensitive subjects in as yet unpublished experiments by the reviewers.

Another condition which furnishes an explanation of persistence and exacerbation of sensitization dermatitis is the contamination of inherently innocent materials by minute amounts of powerful sensitizers or the presence of them as residual traces in otherwise inert masses. Examples of these events are cases where cold creams, deodorants, and other innocent cosmetics became contaminated with nail polish or paraphenylenediamine, to which sensitivities existed, and then were incriminated as causes of the dermatitis (Leider and Furman⁵²). The failure to realize that hand-borne allergens can be widely distributed to other materials permits chronicity of dermatitis to be established by continuous exposure to these contaminated materials despite elimination of the major source of allergen.

Whereas strict avoidance of discoverable allergenic causes is almost always perfectly satisfactory management of allergic eczematous contact-type dermatitis, some patients demand, and some situations would make desirable, a hyposensitization or modification of hypersensitivity by some routine like repeated exhibition of the allergen in graded doses on the skin.

To date we know of no study which shows reversal of epidermal sensitivity to original insensitivity by a feasible and repeatable technique which is effective in 100 per cent of cases. It is probable that the levels of sensitivity in eczematous sensitivity fluctuate spontaneously and sometimes fall to zero after long avoidance of previously exciting allergens and particularly often in the aged. The lesser incidence of poison ivy sensitivity, for example, in older age groups compared to that in youth or young adulthood may reflect this trend. The phenomenon of "hardening" is an-

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other circumstance which perhaps is clinical specific hyposensitization, but it is usually only a temporary immunologic reversal, judging by the frequently observed reappearance of sensitivity after an adequate period of avoidance and then re-exposure. In the study of Witten and Shair¹⁰³ on the effect on the level of sensitivity of repeated application of simple chemical allergens by patch test, no lessening of sensitivity was observed. No consistent or persistent change in degree of sensitivity could be demonstrated. If anything, the level of sensitivity seemed to rise after repeated application of the allergen. These findings even contradict the clinical observation of hardening—at least with respect to the substances they worked with, the quantities used, time intervals of application, et cetera.

The most hopeful method of favorably modifying epidermal sensitization in some cases is by feeding or parenteral injection of corresponding allergen. In cases of poison ivy, ragweed pollen, grass pollen and pyrethrum sensitization there seems to have been some measure of success. Ingraham³⁸ and Slater et al⁸⁷ have reported clinical abatement and decrease of sensitivity, confirming earlier studies, particularly those of Shelmire.³⁷ It is difficult to explain the mechanism of this improvement. Knowing nothing of antibody action in eczematous sensitivity in man, one can but be content for the time being with the satisfactory practical result. In this connection studies by Chase¹⁶ show that in the guinea pig prefeeding with a powerful eczematogenic chemical (picryl chloride) tended to prevent or at least lessen the intensity of subsequent induction of "epidermal" sensitization, but feeding after induction of sensitization did not influence established sensitivity. This finding is in direct contradiction with what apparently happens in the oral and parenteral treatment of plant and pollen contact dermatitis in man.

Many papers have appeared on the value of antihistaminics in allergic eczematous contact-type dermatitis by both topical and oral administration. Mayer⁶¹ conducted a laboratory study on animals and reported results which were interpreted to show favorable effects of Pyribenzamine on experimentally induced contact dermatitis, both from primary irritants and from allergens. However, the doses of antihistaminics used were much larger than those considered permissible in man. Others have reported clinical and statistical studies with variable claims of benefit. The sum total of effectiveness described in all these reports does not impress us. It appears possible that cases of epidermal sensitization as are attended by some degree of urticarial edema have some beneficial effect from antihistaminic therapy. Our own experience is that the effect of antihistaminics in contact dermatitis is purely antipruritic. What impresses us is the increasing number of case reports of eczematous sensitization from "antihistaminics" (see under drug eruptions).

Allergic eczematous contact-type dermatitis is one of the most obvious of allergic transformations. It fulfills every clinical criterion of acquired, specifically altered reactivity. But, at the same time, it is one allergic condition in which the demonstration of antibodies and antigen-antibody interaction has been least possible both *in vitro* and *in vivo*. In the allergy of infection (to be discussed more fully below), in the atopic and anaphylactic varieties of allergic change, there are several methods of demonstrating antibodies and antigen-antibody interaction. In atopy, in anaphylaxis and in the case of the neutralizing antibodies involved in immune states, the presence and sometimes the production of antibodies can be shown by repeatable techniques. They frequently can be isolated and titrated *in vitro*. They can be demonstrated *in vivo* by all sorts of procedures like the Prausnitz-Kustner reaction and modifications of it. In allergic processes due to infectious microorganisms antibodies may be shown like the pro- and anti-cutins of tuberculosis, the reagin and immobilizing antibody (Nelson⁶⁵) in syphilis, et cetera. But in eczematous allergic sensitization much less evidence can be produced. In the older literature modifications of the Prausnitz-Kustner experiment have sometimes been reported to have demonstrated antibodies in cases of eczematous sensitization (Biberstein¹²). For example,

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with the Koenigstein-Urbach method, several experimenters have claimed success in demonstrating something in the blister fluid from areas of allergic dermatitis which can passively transfer eczematous sensitization. The present authors⁵¹ have tried this procedure and have not been able to reproduce the results claimed by others. Again the work of Landsteiner and Chase⁴⁵ and others must be cited as evidence that the carriers and possibly also the producers of antibodies both in eczematous sensitization to simple chemicals and in tuberculin-type sensitivity are certain elements of the leukocytic system, i.e., the monocytes, lymphocytes and plasma cells. Their experiments on the passive transfer of such sensitivities by means of washed cells from peritoneal exudates rich in leukocytes and their^{44,46} and Rostenberg's⁷⁸ experiments on the route of dissemination of epidermal sensitization place the locus operandi in the reticuloendothelial system. A pertinent study in this connection is that of Nexmand,⁶⁶ who examined the cellular content of bullae produced by primary irritants and of those from true allergic dermatitis. He found that the latter had a high lymphocyte count whereas the former contained predominantly polymorphonuclear leukocytes. It is possible that blister fluid with properly high lymphocyte count may be effective material for successful accomplishment of transfer by the Koenigstein-Urbach technique. The bridge between all these studies in animals to sensitization in human beings has been furnished by the successful passive transfer of tuberculin sensitivity accomplished with viable leukocytes by Lawrence.⁴⁷ His source of white cells was the blood stream and 50 c.c. of blood yielded a sufficient amount of cells to effect transferability. It remains to be seen if a similar procedure will be successful in the transfer of eczematous sensitization.

Kalkoff⁴⁰ tried, in the guinea pig, to inhibit spreading of eczematous sensitization from the site of application of the sensitizing agent. Similar to previous work by Landsteiner and Chase, this was done by making a skin island, by excising a band of surrounding skin to a considerable depth, but Kalkoff was unable to prevent the spreading.

Crepea and Cooke¹⁸ succeeded in passively transferring sensitization to poison ivy in guinea pigs by means of washed splenic cells in sixteen of nineteen animals and by means of sera in seven of fifteen instances. While the transfer with splenic cells fits in with previous work by Landsteiner and Chase,⁴⁵ the transfer by means of sera is a novel phenomenon, unless the sera were not entirely cell free.

Hollstrom³⁶ did experiments where patients, subsequent to sensitization to 2-4 dinitro-chlorbenzene, were inoculated with tertian malaria. Thirteen of fifteen such patients did not react to the substance three weeks later. In the not-fever-treated control group, thirteen of fifteen patients showed positive reactions to 2-4 dinitro-chlorbenzene. These experiments are a significant contribution to our knowledge regarding the factors producing changes and fluctuations in eczematous allergies. The use of the term "epidermal" allergy by Hollstrom is not advisable. In view of the fact that it is still unknown where all the various phases of eczematous sensitization take place, it is better to refer to "eczematous allergy." Another interesting experiment in allergic sensitization was done by Haxthausen,³² who tested whether allergic eczematous reaction in a piece of skin interfered with its vitality. Using a modified pinch graft technique, he found no evidence of impairment in vitality of the tissue.

In the histopathogenesis of allergic eczematous contact-type dermatitis, the inflammatory dynamics have long been a matter of study and speculation. Since the epidermis is an avascular structure, it is a question of how and why fluid and cells reach the area in sufficient volume to produce spongiosis, vesiculation and bulla formation plus exocytosis of leukocytes. Polak and Mom⁷¹ studied the problem by special histologic techniques and confirmed the thesis of Civatte that lysis and death of malpighian cells by the allergic process is the quintessential lesion. Following upon this there is variable influx of fluid and cells as a secondary effect from the

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papillary vessels of the underlying true skin. This paper is illustrated by beautiful and convincing high-power photomicrographs which show the stages of the basic and initial epidermal damage. This visualization of the early allergic events in the shock organ is important but still not as important as the biochemistry of the phenomenon would be. However, it may be a forerunner of such humoral elucidation and may be important to such problems as the site of antibody formation, lodgment and interaction with allergen.

Werz¹⁰¹ observed dermatitis due to quinine in a quinine plant in twenty-two workers, i.e., in 10 per cent of the workers. The high incidence was thought due to the employment of a large number of unselected workers after the war.

Higgins and Kindel³³ saw a case of exfoliative dermatitis due to a DDT spray. Patch tests were positive to DDT and two of thirteen chemically related agents. DDT sensitivity was no longer demonstrable two months after healing of the eruption. This is a rather unusual occurrence, as allergic eczematous contact sensitization usually persists for a long period of time. However, allergic sensitizations to certain substances, e.g., penicillin, perhaps tend to become lost more often than sensitizations to most substances.

A case of eczematous dermatitis due to Intracaine is reported by Rein and Kanof.⁷⁶

An apparently allergic eczematous reaction caused by aged silver nitrate solution occurred in a patient of Gaul and Underwood,²⁷ whereas fresh solutions caused no reaction.

Eczema around the waistline and neck occurs in men working in young plantations due to a lichen, *Parmelia Caperata*, which grows on the older trees, according to Tenchio.⁹³ Patch tests with lichen material were positive on sweating skin.

Skinner⁸⁶ recorded a case of allergic eczematous dermatitis due to phenolphthalein. While this agent is an unlikely one to be contacted externally, it is of interest to find it capable of establishing still another type of allergic response in addition to others it is well known for, such as "fixed" eruptions and urticaria. Also, it is another illustration that every simple chemical must be suspect of ability to induce eczematous allergic states. This refers even to chemical elements, as for instance, the case of Robinson and Bereston⁷⁷ in which eczematous dermatitis was traced to mercury in amalgam dental fillings.

Seventy-seven cases of dermatitis due to green summer pascal celery were studied by Wiswell et al.¹⁰² There was some evidence that immunity can be developed. Injections of diluted celery oil in two highly sensitive workers were successful in producing protection.

Another series was reported by Arnold³ where dermatitis due to the light sensitizing effect of parsnips occurred in a military camp in 1940. Patch tests with parsnip material were negative. This type of sensitivity is not based on an allergic mechanism and must be differentiated from allergic contact dermatitis as it is based on a nonallergic photosensitizing effect.

There are three types of adhesive tape irritation, according to Peck et al⁶⁹: (1) a fleeting reaction, due to the trauma of tape removal, (2) a reaction due to specific allergic sensitization to one or more components of the tape—this reaction is rare—and (3) a reaction due to changes in pH and in the bacterial flora under the tape—this is the most common reaction due to adhesive tape. The addition to the adhesive mass of the tape of fatty acid salts, such as zinc caprylate and zinc propionate, reduces the bacterial flora and the degree of change in pH under the tape. Such tape, according to Peck et al, also produces much less skin irritation. However, Gaul and Underwood²⁶ failed to find any difference in irritancy of ordinary adhesive tape and tape containing fatty acid salts.

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ATOPIC DERMATITIS

No fundamental contributions have appeared in the past year on this important and not yet well understood condition. There have been a number of articles on various practical approaches. Particularly the one by Glaser²⁸ is valuable for new readers in the subject and those who want to bring themselves up to date. In the past, and still to a considerable extent today, articles on atopic dermatitis did not convey the great difficulties that exist in the management of very severe examples of atopic dermatitis. A realistic, even if highly discouraging, awareness of this situation can be found in an article by Hill.³⁴ This observer of long experience opens his paper with a statement to the effect that the longer he deals with infantile eczema, the less sure he is of what he is dealing with and of how to deal with it. Like a great many others, particularly dermatologists, he has departed from initial enthusiasm 'for the value of intracutaneous testing with protein allergens and management by elimination of substances that yield positive reactions. He is now at the point of asserting that only the exceptional case is benefited by such a course. For the rest, versatile management of each episode, largely by varied topical medicaments, is the best that can be done. In contrast, Tuft⁹⁶ still believes that there is great value in skin testing, particularly with inhalants in the older age group, and in desensitization with incriminated substances, most frequently dust. Tuft suggests that the best results can be obtained by combination of dermatologic, topical and systemic management plus a thorough work-up and treatment from the viewpoint of allergy.

In this connection it is worthwhile to consider the paper by Narins,⁶³ who called attention to the unreliability of scratch tests in testing for immediate wheal responses in atopic dermatitis. While intracutaneous tests produce repeatable results, scratch tests, even when done by the same person, with the same technique and in the same sites, produce completely unpredictable results.

Nexmand⁶⁶ published a detailed study on atopic dermatitis: 62.5 per cent of twenty-four patients who were worse during the summer gave positive skin tests to pollen extracts, often associated with a flareup of the eruption and hay fever. Only 17.8 per cent of patients who did not get worse during the summer gave positive pollen tests, and only one of these had hay fever. Nexmand states that positive skin tests with food and inhalant allergens are rare in the one-to five-year age group. Positive skin tests with inhalants are much more frequent than those with foods in the age group over five.

A new approach to the atopic dermatitis problem, which has found insufficient attention on the part of allergists and dermatologists is the work by Sulzberger et al⁹⁰ on the possible importance of the "sweat retention syndrome" in atopic dermatitis. These workers found failure of sweating and cutaneous lesions due to plugging of the sweat gland openings, similar to prickly heat, in the histologic sections of some atopic dermatitis patients. This fits in with the well known facts that (1) some atopic dermatitis patients tend to get much more itchy upon physical exercise and exposure to heat, (2) many atopic dermatitis patients show a fine papular eruption over the trunk (plugged sweat pores?) and (3) the marked improvement of atopic dermatitis patients in dry hot climates where the evaporation of sweat is not hindered by high atmospheric humidity. The full clinical evaluation of these findings by Sulzberger et al still awaits further study.

A refreshing approach to the problem of atopic dermatitis in recent years has been that of Simon^{3,51,52} with his work on allergens in human dander, in skin generally, in scales from some dermatoses and in comedones. These allergens give reactions in some subjects with atopic dermatitis and no reactions in normal controls. Patch tests with human dander (50 per cent in petrolatum by volume of the crude material as obtained from combings) give eczematous responses in atopic dermatitis patients about half the time and very few such reactions in normals. We ourselves have been able to confirm this in a small series of cases. Intracutaneous tests with extracts from

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dander, apparently normal skin scrapings, scales and sebaceous concretions give immediate urticarial reactions in Simon's experience. The clinical significance of the patch test and intracutaneous test reactions to these allergens is as yet unknown. That there may be some clinical importance to the dander allergen could be suspected on the basis of the fact that for many years it has been a cardinal rule of dermatologic treatment of atopic dermatitis that scaling and seborrhea of the scalp must be treated in all cases where it is present. In some ways it would be satisfying to explain and excuse one's helplessness with some cases of atopic dermatitis by believing that such patients are sensitive to their very selves, and so being, how can one be effective in such a hopeless situation? We think that Simon's interesting findings also are another confirmation of the well-known capacity of atopics to acquire multiple immediate wheal reactions to allergens similar to the reactivity to egg, wheat, milk, fish, et cetera.

Bartlett⁹ cites a case in which he established by skin test, passive transfer tests and by tests of avoidance and exposure that sensitivity to a specific human scalp dander was present and the sole cause of an allergic dermatitis (atopic dermatitis?). There was no sensitivity to stock scalp dander or to the body dander of the person whose scalp dander elicited the dermatitis.

Charpy¹⁵ administered unsaturated fatty acids, pyridoxine and intestinal vaccines (per os) to 250 cases of infantile eczema, with improvement in 70 per cent. In view of the combination with pyridoxine and vaccine, it is difficult to draw conclusions as to the efficacy of the fatty acid therapy itself. Azerad and Grupper⁵ also gave unsaturated fatty acid to seven patients with infantile eczema, in all of whom recovery ensued. Our own experience with unsaturated fatty acid treatment of infantile eczema and atopic dermatitis in children, adolescents and adults has thus far not aroused great enthusiasm in us for this sort of treatment.

DRUG ERUPTIONS

It is striking how many allergic drug eruptions are aroused by such innocent and relatively nontoxic drugs as the antibiotics and so-called antihistaminics. For example, contrary to a widespread belief, severe and potentially fatal, although extremely rare, erythrodermas can be caused by penicillin. Andrini⁴ relates a case of erythroderma due to penicillin. Specific therapy and at the same time desensitization is said to have been carried out by continued administration of very small doses of penicillin. Another case of exfoliative erythroderma after penicillin, and this one with fatal outcome, was recorded by Rabinovitch and Snitkoff.⁷⁴ However, their evidence that death was due to the penicillin is not conclusive.

Goldman and Farrington²⁹ observed two cases of stomatitis and glossitis after oral administration of penicillin tablets. Isled and Karabadjakian³⁹ claim that they demonstrated a common antigen in *penicillium notatum* and *achorion quinckeum*. The various reactions which can be caused by penicillin are summarized by Black et al¹⁴ as follows: (1) urticarial, (2) vesiculo-bullous, (3) contact dermatitis, (4) serum sickness, (5) stomatitis and pharyngitis, (6) ocular reactions, (7) asthma, (8) angioneurotic edema, (9) purpura, (10) sterile abscesses, (11) headache, fever, vomiting, and (12) questionable reactions as erythema nodosum.

Peck et al⁷⁰ conclude from their studies that in penicillin sensitization the test for delayed tuberculin-type reaction offers a reliable index of sensitivity but that the patch test and test for urticarial response are unreliable. This is in contradiction to Farrington and Tamura²⁵ who utilize 0.1 c.c. of 2.5 to 2,000 units of crystalline penicillin G or K per c.c. in saline as an indicator of urticarial penicillin hypersensitivity.

Touraine and Pichon⁹⁵ observed twenty-three cases of streptomycin eruptions among hospital personnel. The problem of sensitization to various antibiotics has also been studied. Berke and Obermayer¹⁰ patch tested a group of fifty-five nurses

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and obtained 39 per cent reactions to streptomycin, 39 per cent to procaine, 25 per cent to penicillin and 4 per cent to tyrothricin. Another case of rare tyrothricin sensitivity is reported by Goldman, Feldman and Altemeyer.³⁰ The sensitivity crossed over or at least also was present to bacitracin and other antibiotics.

The great number of allergic eruptions due to contact with antihistaminics and the less numerous, but still very important, eruptions due to the ingestion or injection of these "anti-allergic" or "antihistaminic" drugs may have its humorous aspects for those interested in the theoretical background of these substances. However, the reviewers are quite certain that these eruptions and the itching associated with them are not considered jokes by the so afflicted patients. While the application of most "antihistaminic" ointments produces a low incidence of eczematous allergic reactions, a high incidence has been reported for Thephorin ointment by Ellis and Bundick²³ and Howell.³⁷ Other observers, including Laymon and Schmid,^{48,49} report no unusually severe reactions from Thephorin ointment. The experience of the reviewers suggests that Thephorin ointment produces more allergic sensitizations than is allowable for a therapeutic agent with purely antipruritic effects but that the incidence is not as high as the 28 per cent "clinical reactions" in Ellis' series. In the reviewers' opinion, antihistaminic ointments should be used with circumspection and preferably not in cases of allergic eczematous contact-type dermatitis because these latter cases have, as a group, a greater than normal capacity to undergo eczematous sensitization.

London and Moody⁵⁸ record a case of urticaria which was very obviously due to Pyribenzamine from the circumstance that whealing occurred within an hour of exhibition of the drug upon two occasions. Notably, the first occasion of the eruption was, as far as can be told, the very first encounter with the agent. Unless the history is faulty, this would suggest that this urticaria was not on an allergic basis inasmuch as there was no incubation period of sensitization. However, it is more likely that there was a pre-existing sensitization due to exposure to a chemically related agent which was not discoverable in the history.

Rattner and Graffin⁷⁵ report a case of extensive dermatitis proved to be due to orally administered Pyribenzamine by trials of elimination and re-exposure. The case was complicated by a history of previous administration of gold parenterally for arthritis. The Pyribenzamine was given for a pruritic dermatitis of the ears, the nature of which was not specified. After Pyribenzamine was found to be the source of the trouble, Benadryl was administered without event, which is not remarkable, considering that the substances are not chemically related.

One of us (RLB) together with M. Yanowitz has seen a case of urticaria due to Chlor-Trimeton. Bellach¹¹ observed many of the characteristic immunologic phenomena in a case of sulfapyridine hypersensitivity. A case of "fixed" eruption due to sulfadiazine has been studied by Meltzer. Sulfamerazine also elicited the reaction but not para-aminobenzoic acid.

Tolmach and Frank⁹¹ described the first case on record of a "fixed" drug eruption due to bromides. Aguilera and Cadinanos¹ report a case of tuberous iododerma on the face of a breast-fed seven-month-old infant due to transmission of iodine by maternal milk. The mother had been receiving two injections of an iodopeptone compound.

A case of urticaria due to mercupurin was investigated by Gottlieb.³¹ Scratch-patch test produced within two hours an urticarial eruption (not locally at the test site) and a papular erythematous eruption at the test site after twenty-four hours. Salyrgan-Theophylline produced a similar reaction in a scratch-patch test. Dobkevitch and Sidi²² noted a case of eczema of the face due to a collyrium of atropine sulfate.

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URTICARIA

As for atopic dermatitis, no new or fundamental studies have appeared on urticaria. This subject, together with atopic dermatitis, and to a less extent the rest of the field of allergy, suffers more year by year from indiscriminate psychosomatic explanation.

The only tangible advances have been in the further development of the heterogeneous group of compounds which have therapeutic kinship in their suppressing effect on the mechanism of whealing. There has been less emphasis lately on straight histamine antagonism as an explanation of their action, although the attractiveness of the histamine theory as the basis of some forms of allergic hypersensitivity still appears to be great for some workers.

Despite the sometimes miraculous effect of the anti-urticular agents, no deep satisfaction derives from them in definitive management of urticaria similar to many cases of allergic rhinitis, asthma, et cetera. It is true that they effectively carry over the patient in acute, self-limited urticaria; and in some cases of chronic urticaria they reasonably control whealing and/or itching so long as they are taken constantly. But rarely is the patient, or the medical advisor, content with such continuous medication, even though usually harmless. One is still left with the problem of etiologic resolution.

What is still urgently required are studies on large series of cases of urticaria with statistical and other data on what percentage is ultimately proved to be allergic, what fraction nonallergic. And of those that can be proved allergic, how many can be shown to be due to (1) foods, (2) drugs, (3) inhalants, (4) bacterial allergens, (5) physical agents, (6) autochthonous materials and other agents.

Wadulla⁶⁸ saw a case of urticarial eruptions on both legs due to ultra-short wave therapy on the right leg. The eruption on the left leg was explained on the basis of a reflex mechanism. In Polano's⁷² case sun exposure produced wheals, fall in blood pressure, shock and collapse. A similar condition was present in other members of the family.

ERUPTIONS DUE TO INSECTS AND PARASITES

Many, if not all, cases of papular urticaria are actually due to insect bites. This has been shown by Shaffer, Spencer, and Blank.⁸⁰ Many cases of papular urticaria are cured by use of a lotion containing 5 per cent DDT; and patients with papular urticaria give a much higher incidence of positive skin tests to extracts of fleas and bedbugs than groups of control patients without papular urticaria.

Carpet beetles can cause eruptions of papulo-vesicular and urticarial character, as shown by a case of Cormia and Lewis.¹⁷ Larvae hairs produced a local reaction and a distant cutaneous response.

Eruptions due to contact with moths were seen by Hill et al³⁵ in three members of a tanker crew. The lesions were papulo-vesicular, erythematopapular and urticarial in character. Patch tests were positive.

Schoch⁷⁹ states that of 100 unselected patients tested with ascaris allergen 55 per cent showed positive immediate wheal responses. Desensitization was attempted in eight patients, with some improvement in their dermatoses. Schoch's figures indicate that the skin test with ascaris antigen, at least in his group of patients, is not of diagnostic value. This comes as no great surprise, as sensitization to one helminthic parasite is known to bring on skin sensitization to the extracts of other helminths as well.

THE ALLERGY OF INFECTION

In the recent past there has been a rekindled interest in the allergy of infection,⁹² particularly as represented by the disease processes of syphilis and tuberculosis. The concept of the "id" and the explanation of some effects of infectious diseases by autosensitization to injured body-own tissue have received considerable attention.

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In the case of syphilis, even the attainment of apparently successful and permanent cure with penicillin has not made theoretical considerations seem superfluous as shown by the new work of Nelson and others on spirochete culture, immobilizing antibodies, new serologic techniques and related phenomena. But especially in the case of tuberculosis and allied diseases, where no entirely satisfactory antibiotic therapy is available, the allergic states engendered by them, the clinical expressions of those allergic states and finally the meaning of those allergic states in terms of protection (immunity) or harmfulness (disease) are ever timely subjects for study.

About ten years ago, Kveim⁴¹ set into motion a great deal of new work and speculation on the relation between tuberculosis and sarcoidosis by describing a novel skin test for sarcoidosis. The test material is an "antigen" processed (in a manner similar to Frei antigen) from histologically proven human sarcoid tissue. A positive reaction to the intracutaneous deposit of this material consists of a delayed papular to ulcerous lesion (weeks to months after injection) which upon microscopic examination shows sarcoid structures. Such positive reactions are said to occur only in patients suffering from sarcoidosis in one of its many forms (Boeck's disease, Schaumann's disease, Jungling's disease, Heerfordt's disease, et cetera). Kveim interpreted his findings as proving that sarcoidosis is a disease entity *sui generis*, i.e., of unknown cause but definitely not of tubercle bacillus causation. For some fifty years prior, debate had raged on whether sarcoidosis is a disease *sui generis* or whether it is merely a reaction form, i.e., whether it is an expression of various infectious diseases, particularly tuberculosis. The likelihood that at least many cases of sarcoidosis are in some way connected with tuberculous infection had been established by the positive anergy to tuberculin (see below) which is demonstrable in many cases of sarcoidosis. The Kveim test has by no means settled this issue; in fact, it has given new impetus to experiment and argument. The correctness of Kveim's observations concerning the skin test has been amply confirmed by many observers, namely, abroad by Danbolt,²⁰ Lomholt⁵⁷ and Putkonen⁷³ and in this country by Nelson⁶¹ and Leider.⁵⁰ However, there is no agreement as to the relative specificity of this test which is now generally called "Kveim test." The interpretation of the test by the above workers is also still a matter of dispute among them, as is the background question of the relationship between sarcoidosis and tuberculosis.

In a re-examination of the subject, Leider⁵⁰ found that at least two observers before Kveim showed that characteristic reactions could be obtained in sarcoidosis with tubercle bacilli. Lemming^{55,56} accomplished this with BCG vaccine, and Warfvinge^{99,100} did the same with living virulent human tubercle bacilli. The reactions they obtained were clinically and histologically compatible with natural sarcoid. Following all of these leads, Leider and Sulzberger⁵⁴ and Leider and Hyman⁵³ undertook to study the clinical, immunologic and histologic responses of the skin to BCG vaccination in various categories of tuberculin sensitivity in man. Certain theoretical considerations suggested that several different types of clinical, immunologic and histologic responses would occur, depending on the nature of the tuberculin reactivity present, and in particular that the peculiar lack of tuberculin reactivity in many cases of sarcoidosis would produce characteristic and distinctive results. The gist of this work may be summarized as follows: There are four distinguishable conditions of tuberculin reactivity, namely:

1. Native or original anergy (no reaction, even to concentrated tuberculin) which is the nonreactive status with respect to tuberculin that exists in man and many lower animals prior to adequate exposure to the tubercle bacillus.
2. Normergic and hyperergic reactivity to tuberculin (reaction to tuberculin up to dilutions of 1:10,000) which are the common sensitive states that come into being after adequate exposure to the tubercle bacillus. These reactivities are allergic transformations.

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3. Positive anergy or relative hypoergy (no reaction to tuberculin 1:100 up to undiluted tuberculin) which is comparative insensitivity to tuberculin that sometimes ensues after infection with, or adequate exposure to, the tubercle bacillus. Positive anergy is different in quality from native or original anergy in that it is not a return to aboriginal insensitivity but rather is progression into another acquired, specifically altered capacity to react to the tubercle bacillus and/or its products. In other words, positive anergy is another allergic transformation but one in the direction of lesser reactivity and possibly after a previous condition of normergic or hyperergic reactivity.

4. Negative, nonspecific or absolute anergy which is transient nonreactivity to tuberculin that is induced by certain intercurrent febrile diseases and cachectic or debilitating states. It is not a true immunologic status but rather a passing expression of interference with established immunologic phenomena by incidental and repressive factors. In the condition of nonspecific anergy, reactivity to other tuberculin-type allergens, to wit, trichophytin, Frei material, et cetera, is also abolished or suppressed if such reactivity was previously existent. In short, established reactivity to tuberculin-type allergens continues to exist in potential during the condition of non-specific anergy and reasserts itself if and when the repressive factors disappear.

In addition to these four forms of reactivity to tuberculin previously published, there must be considered a fifth form which occurs in the aged. In many aged persons tuberculin sensitivity is absent despite the fact that, at least in some of them, it had presumably been present at a previous time. This type of anergy in the aged has not yet been adequately studied from an immunologic viewpoint, and because of this it will be left out from further discussion in the present review. Individuals exhibiting any one of the first three categories of tuberculin reactivity respond clinically, immunologically and histologically to BCG vaccination in the following manners:

1. A subject who is natively or originally anergic to tuberculin responds to BCG vaccination with the first part of Koch's fundamental experiment, i.e., with an incubation period of some two weeks and then with an overt reaction of erythema through papulovesication, pustulation and ulceration to healing by scar in two to three months. Demonstrable tuberculin sensitivity comes into being at about the expiration of the incubation period. Microscopically the reaction is marked by banal polymorphonuclear inflammation in all the early stages of the evolving lesion and eventual appearance of tuberculoid structures toward the very end of it.

2. A subject who is already normergic or hyperergic to tuberculin responds to BCG vaccination with the second part of Koch's fundamental experiment, i.e., within a reaction time of twenty-four to forty-eight hours and then with an accelerated course of erythema, ulceration and scar-healing in some two to six weeks. Tuberculin sensitivity remains usually unchanged by merely one such vaccination. The histology of this reaction is in an early brief stage a banal inflammation and then rapid appearance of tuberculoid structures in later stages.

3. A subject who is relatively hypoergic or positively anergic, i.e., who is insensitive to tuberculin in the specifically acquired manner, responds to BCG vaccination with a papule that begins to become perceptible in about one week and then tends to last indefinitely as a torpid, non-caseating papule or as a slowly growing sarcoid-like plaque. Relative tuberculin insensitivity is usually not influenced by a single BCG vaccination. The histology of this reaction shows essentially and predominantly tuberculoid structures. The process is productive, proliferative and infiltrative with epithelioid cells.

The conclusions drawn by Leider, Sulzberger and Hyman from these studies are as follows:

1. The clinical courses of the responses of the skin to BCG vaccination in various categories of tuberculin sensitivity are characteristic and distinct.

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2. The immunologic change from native or original anergy to normergic or hyperergic reactivity to tuberculin is particularly sharp and repeatedly demonstrable in proper subjects. The persistence of established reactivity and of established positive anergy to tuberculin are also repeatedly demonstrable phenomena.

3. The histologic pictures of the reactions to BCG vaccinations of the various categories of tuberculin sensitivity are not as finely distinctive as the clinical and immunologic events. Nevertheless, there is in these reactions a general trend of histologic progression from intense banal inflammation in the earliest tissue response to the tubercle bacillus in the natively anergic subject, followed by fairly classical tubercle formation in established hyperergic and normergic (tuberculin-positive) subjects and eventually to sarcoid-like pictures in subjects who become positive anergic.

Björnstad¹³ and Danbolt,¹⁴ whose experimental findings virtually duplicated the ones listed above in nearly every respect, arrived at entirely different conclusions. It appears possible now that all the results can eventually be reconciled and welded into a unitary theory of allergic transformation in the diseases marked by granulomatous processes.

Another important aspect of the allergy of infection, as it applies to dermatology, is the concept of "bacterids." It may be useful to examine for a moment what precisely is meant by the suffix "id." First, if we may be permitted another pedantic digression, it can be pointed out that the ending is a contraction of the Greek "ides" and has the force or meaning of "family relationship." In a proper name it means "son of" as in Christophorides (son of the Christ bearer) and is equivalent to O', Fitz,-son,-sen,-off,-witz, et cetera. Thus in words of general and not particularly technical context it carries the simple meaning of class relationship as in spermatid, fluid and liquid. The same applies to uses like leukemid, carcinomatid, et cetera. In uses in connection with certain infectious processes taking place in the skin the term has acquired connotations of allergy; thus Sulzberger defines an "id" as a secondary manifestation appearing in allergic tissue and produced by the microorganism and/or its products emanating from a remote focus.

In bacterid, the narrowed meaning here applies to eczematous and other lesions that result as a secondary manifestation appearing in allergic tissue and produced by ordinarily pyogenic organisms, particularly staphylococci and streptococci and/or their products emanating from a remote focus. Andrews² and Epstein have written extensively on the occurrence of this type of event in recent years. Proof usually consists in demonstrating the presence of microorganisms on culture in sites that have reputations as foci of infection and the clinical disappearance or remission of the eruption upon eradication of the focus of infection or upon specific desensitization to the particular microorganism. Such circumstantial evidence seems often convincing but not always, especially when the number of cases is small or when clinical improvement is only partial or not dramatic. Moreover, the question always remains unanswered whether the focus of infection was the cause of the eruption or was merely a contributory factor. However, Storck¹⁵ reports experiments and skin tests to support the thesis that certain eczematous processes are the result of specific sensitization to products of bacterial pathogens. Implicated organisms in their order of frequency were found to be *staphylococcus aureus*, *streptococcus hemolyticus* and the colon bacillus. The significance of his findings is lessened by the fact that a high percentage of reactions was produced also in patients with normal non-eczematous skin. But Storck points out that the number of microorganisms present on the skin is much greater in some eczematous lesions than on normal skin. Particularly in acute exudative seborrheic dermatitis, coin-shaped mycosisiform eczema and in eczematized neurodermatitis is the bacterial count quite high. It certainly appears possible that the eczematous sensitivity to the microorganisms could be a primary and perhaps more often a secondary factor in the production and maintenance of some eczematous lesions. This is especially true because a clinical parallelism can

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be drawn between the classical allergic eczematous dermatitis from simple chemicals and such infectious processes as fungous infections. For example, the clinical picture in dermatophytosis is often predominantly epidermal, and as Sulzberger⁸⁹ has pointed out many years ago, the evolution and progression of superficial fungous infections sometimes appears as if they were based on sensitization effects similar to those caused by inanimate, simple chemical agents.

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962 Park Avenue (Dr. Baer)
820 Caton Avenue (Dr. Leider)

EPINEPHRINE IN THE TREATMENT OF MIGRAINE

(Continued from Page 127)

The eighth patient was a thirty-two-year-old man who had migraine for three years. Excessive amounts of wheat or chocolate could bring on an attack. He suffered from hemicranial syndrome. He was seen in one attack which was relieved by epinephrine in two doses of .05 c.c. Ergotamine had never helped either hypodermically or orally.

The ninth and tenth patients were supposed to have had migraine for three and five years, respectively. They had not responded to ergotamine and failed to respond to epinephrine also. The history was suggestive of migraine, but after a physical workup we found the patients to both be suffering from sinusitis. They had penicillin-sensitive organisms and responded to treatment. These cases illustrate the fact that one must be very careful about making the diagnosis of migraine and not accept too credulously previous diagnoses.

SUMMARY

Eight migraine patients had relief from small doses of epinephrine. In six of these the drug was considered more satisfactory than ergotamine. In the strength of dosage employed, no side effects were noted. If one accepts the concept of vasodilation as the pathologic physiology of the cranial vessels in migraine headaches, then epinephrine in small dosages is worthy of trial.

IN MEMORIAM

WILLIAM BYRON BLACK



WILLIAM BYRON BLACK, 57, A.B., B.S., M.D., was born at Windsor, Missouri. He received his high school and college education at Lamar, graduating from the Lamar College in 1914. He graduated from the University of Kansas Medical School in 1922, and his postgraduate studies were numerous. He taught at the Kansas City Municipal Hospital Department of Otolaryngology for nine years and at the University of Kansas Hospital Clinical Department of Ophthalmology for eight years. At the time of his death he was teaching at the Kansas City Municipal Hospital and Menorah Hospital Ear, Nose, Throat Cancer Clinics. He was attending surgeon at the Kansas City Municipal Hospital, E.N.T. Charity Service, Menorah Hospital; and in the Ophthalmological Department, Kansas University, 1923-1931. He was a member of the Jackson County Medical Society and the Missouri State Medical Association. He was a member of the Menorah, Saint Joseph, Kansas City Municipal and Wesley Hospitals, and St. Vincent's hospital staffs. Doctor Black was past president, secretary, and treasurer of the Kansas City Southwest Clinical Society. He was a Fellow of the American Academy of Ophthalmology and Otolaryngology, American Medical Association, American College of Surgeons, American Triological Society, American Society of Ophthalmologic and Otolaryngologic Allergy, Diplomate American Board of Otolaryngology, and also a Fellow of the American Association for Advancement of Science. Doctor Black contributed a number of articles to important medical journals.

The passing of Doctor Black is a great loss to medicine. He was an inveterate worker and one of the most capable in his specialty. He practiced Ophthalmology as well as Otolaryngology. He attended practically every special graduate course offered in this country, consequently was adequately trained in allergy, bronchoscopy, plastic surgery, and fenestration surgery. He was one of the founders of the Kansas City Anatomic Society and played a great part in the development of this organization, which is one of the best in existence. For many years he was active in the Kansas City Society of Otolaryngology. He was one of the original organizers of the American Society of Ophthalmologic and Otolaryngologic Allergy and the Hansel Foundation, of which he was president at the time of his death.

The College, through the Board of Regents of which he was a member at the time of his death, extends to Mrs. Black and family its deepest sympathy in their bereavement. The death of Doctor Black is a great loss, not only to the College and to those who enjoyed his friendship, but also to the entire medical world, many of whom derived so much benefit through their contacts with him. Doctor Black was a true friend, a grand fellow, well-liked and admired. His friends will miss him. His memory lives on.

His survivors are: his widow, Mrs. Helen T. Black of Kansas City, Missouri, and two sons, Burrill M. Black of Johnstown, Colorado, and William Byron Black, Jr., of Houston, Texas.

IN MEMORIAM

ARTHUR C. KALISCH

Arthur C. Kalisch, M. D., charter member of the Pennsylvania Allergy Association and member of the American College of Allergists died suddenly Wednesday, October 5, 1949, at his home in York, Pennsylvania, as a result of a cerebral hemorrhage.

Dr. Kalisch was born in York, Pennsylvania, on July 22, 1906, and attended the York High School where he was the salutatorian. His collegiate and medical training was at the Johns Hopkins University and medical school, graduating in 1928 and 1932, respectively. He interned at the Jewish Hospital in Brooklyn, New York and had a residency in pediatrics there in 1933. He completed a residency in medicine at the Mt. Sinai Hospital in Baltimore, Maryland, in 1934 and a residency in pathology at the Montefiore Hospital in Bronx, New York, in 1935. He opened offices for practice in York in 1937.

Dr. Kalisch was an assistant in medicine and worked in the allergy clinic at Mt. Sinai Hospital in Baltimore. He attended instructional courses of the American College of Allergists, New York Postgraduate School and American College of Physicians. He was Chief of the Allergy Clinic at the York Hospital and instructor in Allergy in the school of nursing.

He was a fellow of the American Medical Association, member of York County and Pennsylvania Medical Societies. He was a member of both the American Academy of Allergy and The American College of Allergists. He belonged to the University Club of York. Stamp collecting was a hobby.

While in the armed service in World War II, he published a survey of allergy in the Mediterranean theatre of Operations.

Dr. Kalisch is survived by his wife, Harriet, and a son, Arthur C. Kalisch, Jr., aged eight. His death was a shock to all members of the Pennsylvania Allergy Association and other organizations. The College has lost a very active and valuable member, and the officers extend their deepest sympathy to the family.

Mrs. Kalisch, in reply to a letter of condolence wrote: "I hope the College will continue to maintain its high standards in Allergy—to which my husband dedicated his life."

THE PARENTERAL USE OF NEO-ANTERGAN

(Continued from Page 71)

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News Items

CLEVELAND ALLERGY SOCIETY

At a recent meeting of the Cleveland Allergy Society, the following officers were elected for the coming year: President, Dr. Joseph L. Vinocur; Vice President, Dr. Lewis E. Abram; Secretary-Treasurer, Dr. Benjamin Nozik.

SOUTHWEST ALLERGY FORUM

The annual meeting of the Southwest Allergy Forum will be held at the Hotel Peabody, in Memphis, on April 2, 3, and 4, 1950. The local allergy society, the Midsouth Allergy Forum, will act as host for the Southwest meeting.

LOS ANGELES SOCIETY OF ALLERGY

At the meeting of the Los Angeles Society of Allergy held November 25, 1949, the following officers were elected: President, Frank G. Crandall, Jr., M.D.; Vice-President, M. Coleman Harris, M.D.; and Secretary-Treasurer, Norman M. Shure, M.D.

MEXICAN SOCIETY OF ALLERGISTS INSTRUCTIONAL COURSE IN ALLERGY

The Mexican Society of Allergists conducted an Instructional Course in Allergy from January 30 to February 18, 1950. This course was sponsored by the Graduate School of Medicine of the National University of Mexico.

The Mexican Society of Allergists held its Fourth National Congress on Allergy from February 6 to 11.

AMERICAN COLLEGE OF CHEST PHYSICIANS

The First International Congress on Diseases of the Chest will be held at the Carlo Forlanini Institute, Rome, Italy, September 17-20, 1950, under the auspices of the Council on International Affairs of the American College of Chest Physicians and the Carlo Forlanini Institute, with the patronage of the High Commissioner of Hygiene and Health, Italy, in collaboration with the National Institute of Health and the Italian Federation Against Tuberculosis.

Physicians who are interested in attending the Congress should communicate at once with Dr. Chevalier L. Jackson, Chairman of the Council on International Affairs, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois, U.S.A., or with Professor A. Omodei Zorini, Carlo Forlanini Institute, Rome, Italy.

STERILITY AWARD

The American Society for the Study of Sterility is offering an annual award of \$1,000, known as the Ortho Award, for an essay on the result of some clinical or laboratory research pertinent to the field of sterility. Competition is open to those who are in clinical practice as well as to individuals whose work is restricted to research in basic fields or full-time teaching positions. The prize essay will appear on the program of the forthcoming meeting of the American Society for the Study of Sterility, which is to be held at the Sir Francis Drake Hotel in San Francisco on June 24 and 25, 1950.

Full particulars may be obtained from the Secretary, Dr. Walter W. Williams, 20 Magnolia Terrace, Springfield, Massachusetts. Essays must be in his hands by April 1, 1950.

NEWS ITEMS

PSYCHOTHERAPY COURSE FOR ALLERGISTS

Dr. Sandor Rado, Clinical Professor of Psychiatry, and Director of the Psychoanalytic Clinic for Training and Research, Columbia University, will give a course for qualified physicians, entitled, "Psychotherapy for Allergists," beginning Monday, November 6, to Friday, November 10, 1950. This course is being given with the co-operation of The American College of Allergists. Other members of the staff of the Psychoanalytic Clinic will also participate in the program of the course. Lectures and clinics will be held from 9:00 a.m. to 12:30 p.m. and from 2:00 p.m. to 5:00 p.m. daily. It is possible that evening round-table discussions may be arranged.

The purpose of this course is to increase the physician's understanding of the human organism by blending the elements of psychodynamics with the basic medical sciences upon which this understanding rests. An attempt will be made to discuss emotional maladjustment as a factor in the comprehensive pathology of the allergic patient; to familiarize the physician with the psychological aspects of the patient-physician relationship and with the techniques of the minor psychotherapy of the allergic patient.

Physicians practicing in the field of allergy will be given preference in the order of application. Registration will be limited to fifty students. The registration fee is \$100.00. Details may be obtained from Dr. Harold A. Abramson, 133 East 58th Street, New York, New York.

PITTSBURGH ALLERGY SOCIETY

At the regular meeting of the Pittsburgh Allergy Society, held November 21, 1949, the following officers were elected for 1950-1951: President, Dr. Mayer A. Green; Secretary-Treasurer, Dr. Sylvia M. Wechsler. The following committee members were appointed: Executive Committee—Dr. L. H. Criepl, Dr. J. A. Mansmann, Dr. L. L. Bartlett, and Dr. M. A. Green; Membership Committee—Dr. Florence Kline, Chairman; Dr. Philip Blank, and Dr. R. G. Hamilton; Program Committee—Dr. A. R. McCormick, Chairman; Dr. J. W. Hampsey, Dr. L. J. King, and Dr. J. W. Schoolnic; Pollen Committee—Dr. E. P. Claus, Chairman; Dr. J. A. Mansmann, Dr. R. W. Wilson, and Dr. A. H. Neidorff.

* * *

The Allergists Supply Company, 458 Broadway, New York City, announces the development of a new process for graduating their Allergy Barrels and all glass Tuberculin Syringes, which will help reduce breakage.

* * *

I. Wiener, M.D., F.A.C.A., announces the opening of offices at 13011 West McNichols Road, Detroit, Michigan, for the practice of Allergy and Internal Medicine.

EMOTIONAL TRAUMATA

(Continued from Page 107)

5. Miller, Hyman, and Baruch, Dorothy W.: Psychosomatic studies of children with allergic manifestations. I. Maternal rejection: a study of sixty-three cases. *Psychosom. Med.*, 10:275-278, (Sept.-Oct.) 1948.
6. Miller, Hyman, and Baruch, Dorothy W.: A study of hostility in allergic children. Presented at the annual meeting, American Orthopsychiatric Association, Chicago, April, 1949.
7. Miller, Hyman, and Baruch, Dorothy W.: Maternal rejection in allergic children. Presented in the Round Table on Pediatric Allergy at the annual meeting, American College of Allergists, Chicago, April, 1949.
8. Mitchell, J. H., and Curran, C. A.: A method of approach to psychosomatic problems in allergy. *West Virginia M. J.*, 42:1, 1946.

201 S. Lasky Drive

JANUARY-FEBRUARY, 1950

BOOK REVIEWS

POLLEN SLIDE STUDIES. By Grafton Tyler Brown, M.D. 122 pages. Illustrated, \$6.00. Springfield, Illinois: Charles C. Thomas, 1949.

This compact manual is a graphic description of hay-fever pollens, molds and smut spores, based upon years of careful observations by an expert in this field.

The student of allergy requires no previous botanical knowledge, since the photomicrographs, accompanied by brief descriptions, are adequate for the identification of pollen in the dry state, as well as accurate sketches of their appearance through the oil immersion lens from specimen slides, with 182 separate drawings of pollen grains and fungus spores in addition to thirty-four photomicrographs in an effort to reproduce what is actually seen under the microscope.

This book comprises an atlas of the important hay-fever pollen grains and larger fungus spores that are present in the air sufficient in amount to produce symptoms. Doctor Brown reports a complete pollen, mold and smut count in Washington, D. C. in 1938 and 1941. Those who wish to do their own pollen counting with this easy identification, not only of the pollens but of the atmospheric molds and smuts, will find this manual easy to follow. Unlike the textbooks, the author wisely does not include any other material in this handbook. The various genera of pollen grains are described by marginal notes indicating the distinguishing characteristics of each.

The publishers are to be congratulated on the illustrations bringing out the details of identification which are also augmented by diagrammatic sketches.

The influence of weather upon pollination, the preparation of slides and the simple method of counting atmospheric pollens are presented in a short, concise manner in separate chapters. Although these studies report only one locality, the information in this handbook enables doctors or technicians to make reliable pollen counts in any locality.

The references cover the subject well, and there is an index embracing both the botanical and the common names of offenders. The manual embraces all of the essentials which one obtains only through the reading of many books on the subject, so arranged that it makes it a handy reference book containing the full particulars required for proper identification. The busy allergist interested in pollen counting and the identification of pollens and spores will find this book a very handy desk reference.

REMARKS ON THE THEORIES OF ANTIBODY FORMATION

(Continued from Page 116)

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ANNALS of ALLERGY

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ADRENOCORTICOTROPIC HORMONE (ACTH)

Its Effect in Bronchial Asthma and Ragweed Hay Fever

By

THERON G. RANDOLPH, M.D., F.A.C.A.

and

JOHN P. ROLLINS, M.D.

Chicago, Illinois

RELIEF of chronic bronchial asthma following the administration of adrenocorticotrophic hormone (ACTH) was first observed by us in June, 1949; this occurred in a case of advanced rheumatoid arthritis³ complicated by bronchial asthma. The ability of ACTH to bring about improvement in chronic allergic symptoms was not surprising in view of its specific action in rheumatoid arthritis.² Zeller¹⁸ recently reported clear-cut evidence that rheumatoid arthritis responds favorably to the elimination of specific food allergens and reviewed earlier contributions in respect to the allergic concept of this disease. Our clinical experience not only confirms the specific etiology of food allergens in arthritis, but we have also observed improvement in such cases following the specific diagnosis and treatment of inhalant allergy.^{6,9}

These preliminary observations led us to study the effects of ACTH in bronchial asthma and other allergic syndromes. Pilot observations were made on three patients with chronic asthma, preliminary observations of which have previously been reported.¹³ The clinical response of these three patients, whose histories are herewith reported in detail, prompted an evaluation of ACTH in the treatment of other allergic syndromes.

Patients with severe perennial bronchial asthma, refractory to conventional allergic management including prolonged periods of hospitalization, were selected for this study. They were hospitalized and the following determinations were made during a period of forty-eight hours prior to,

Dr. Randolph is an instructor in internal medicine and Dr. Rollins is a research fellow in internal medicine, Northwestern University Medical School.

The ACTH for this study was kindly furnished by Dr. John R. Mote, Armour Laboratories, Chicago.

Presented at the Sixth Annual Meeting of the American College of Allergists, January 15-18, 1950, St. Louis, Missouri.

during the interval of administration of ACTH, and for several days thereafter: (1) The average of three maximum expirations was taken as the vital capacity, charted in the forthcoming figures by the upper solid line. (2) The time required to exhale an arbitrarily selected volume of air, the amount being chosen in relation to the patient's vital capacity and measured in terms of the cubic centimeters of air expired per second, was designated the expiratory rate. This technique, modified after that originally described by Hamburger,¹ will be described in detail elsewhere.¹⁷ The expiratory rate is plotted in the figures as the second (broken) line. (3) The absolute number of circulating eosinophils per cu. mm. of blood was determined by employing the direct counting chamber glycol stain technique previously described⁵; it is shown graphically by the lower solid line. (4) Individual food tests^{8,14} with known food allergens were performed within a three week period prior to hospitalization and repeated either during the course of or immediately following the administration of ACTH. (5) All epinephrine was discontinued for twenty-four hours immediately prior to the administration of ACTH, and aminophylline was administered as necessary for the relief of severe asthma.

Inspiratory and expiratory chest x-ray films were made prior and after the full therapeutic effect of ACTH had been obtained.

Case 1.—C. P., unemployed male, aged forty-three, developed acute sinusitis in December, 1942, which continued throughout the winter. In March, 1943, he developed his initial attack of bronchial asthma which continued for a month until the onset of lobar pneumonia. During the period of and for a month following his pneumococcus infection he remained free of asthmatic symptoms. Severe bronchial asthma then recurred and has been present perennially to an incapacitating degree since this time except for temporary relief obtained during prolonged fasting. In 1945 all food was avoided for a twenty-one day period; after the eleventh day he remained completely free of asthma and rhinitis, was able to walk between two and five miles daily and lost a total of 21 pounds in weight. Three days after returning foods to his diet he had recurrence of his formerly severe rhinitis and asthma.

He has received many types of treatment, including repeated polypectomies, bilateral Caldwell-Luc operation, radium therapy of the sinuses, x-radiation of the lungs, and repeated attempts to diagnose and treat inhalant and food allergy.

Although we have been able to show by experimental individual food tests^{8,14} that the ingestion of each of several major allergenic foods would cause a sharp accentuation in his asthma and their complete avoidance would bring about some improvement, he has never obtained sufficient relief of asthma to be able to earn a livelihood. Although known to be dust sensitive clinically, each attempt to diagnose or treat his house dust allergy has resulted in an accentuation of symptoms, regardless of the exceedingly low levels at which therapy was instituted.

One week prior to hospitalization in August, 1949, an individual food test with orange was followed by a marked accentuation of his chronic asthma.

Figure 1 shows the serial observations of his ventilatory capacity and eosinophil levels prior to, during and following the administration of 225.0 mg. ACTH, given in 25.0 mg. doses every six hours. One should note the initial increase in eosinophils prior to starting treatment which occurred with the cessation of epinephrine administration. In order to keep these initial observations constant, he was maintained on his formerly restricted diet prior to and following therapy with ACTH. His sense

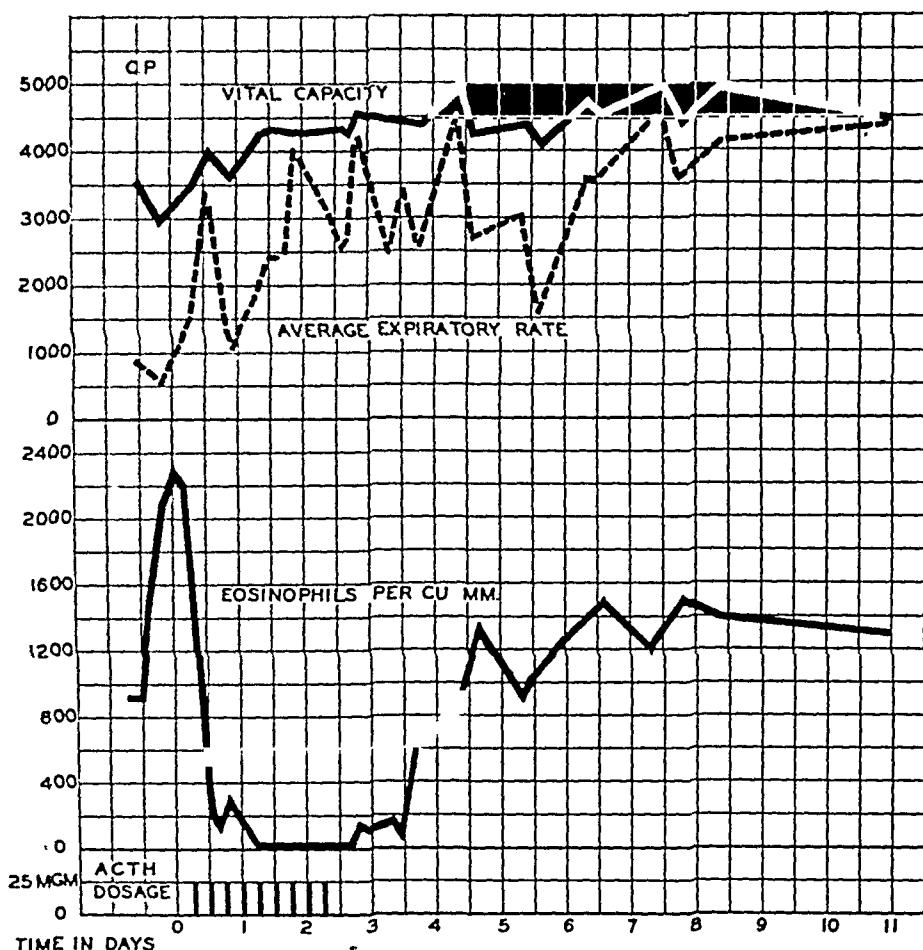


Fig. 1. Variations in the vital capacity, expiratory rate and peripheral blood eosinophils in C.P., a patient with bronchial asthma, following ACTH therapy.

of smell recurred, his nose became patent and he had complete relief of his rhinitis and asthma within twenty-four hours after starting therapy with this hormone. Although relative anosmia recurred after four days, he remained without troublesome allergic symptoms and required no symptomatic measures for their relief during a total period of three weeks. At the beginning of the fourth week from the time of starting therapy his asthma recurred, and in spite of the use of symptomatic measures it reached its former degree of severity within a week.

The experimental ingestion of orange failed to produce allergic symptoms when fed during the course of therapy and again when fed four days after the cessation of ACTH. There was no change in his skin test response to house dust as measured by serial dilution testing^{6,15} after ACTH therapy as compared with identical tests before treatment. Whereas intradermal skin testing with house dust extract (Endo) prior to the administration of ACTH had been followed by a constitutional reaction on each of three different occasions, repetition of the procedure failed to produce symptoms immediately after treatment with ACTH.

A month after the first course of ACTH he was again hospitalized at which time he was having asthma of the former degree of severity. He was given an identical course of ACTH and responded in a similar manner even though returned to a general, unrestricted diet immediately after the cessation of therapy. He remained

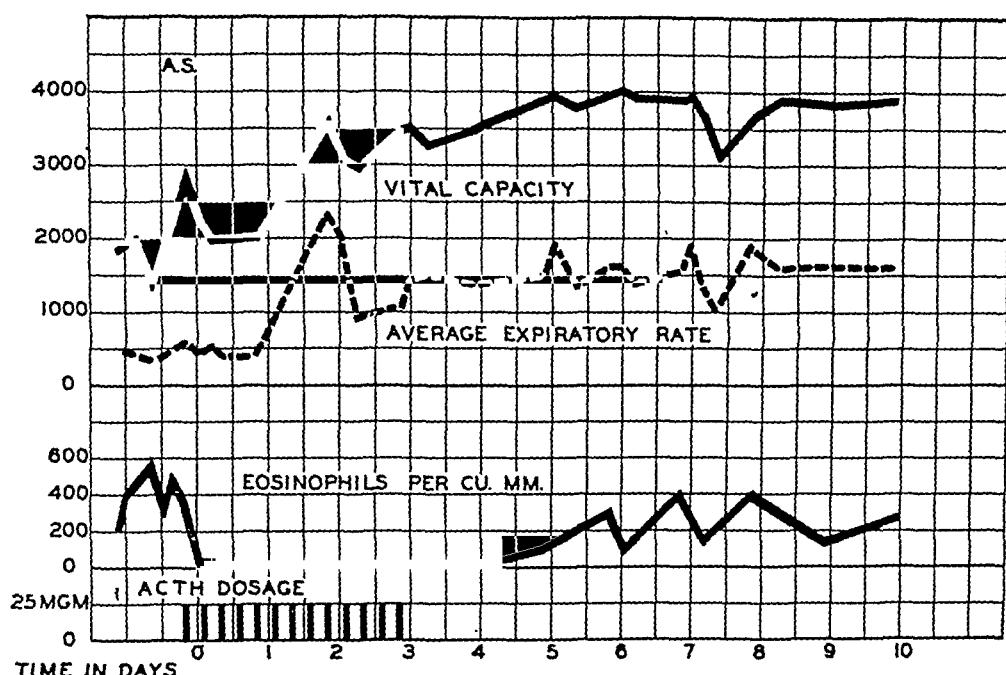


Fig. 2. Variations in the vital capacity, expiratory rate and peripheral blood eosinophils in A.S., a patient with bronchial asthma, following ACTH therapy.

free of asthma and other allergic symptoms for a period of two and one half weeks.

This course of events has been repeated two additional times. During the third course he obtained less effective relief and on his own initiative returned to his former restricted diet. Under these circumstances he remained free of troublesome asthma for a period of three weeks although the occasional use of epinephrine by inhalation was necessary for relief of mild symptoms.

During the fourth course of ACTH in the same dosage he chose to follow his restricted diet and was more satisfactorily relieved of allergic symptoms than during the third course of therapy.

Case 2.—A. S., retired farmer, aged seventy-five, had been subject to perennial bronchial asthma since the age of sixty-two years. His most troublesome symptoms occurred between four and six in the afternoon and during the night, although he had some asthma continually, in spite of large doses of aminophylline, epinephrine, and oxygen by inhalation several times daily. He had been subject to hay fever during the mid and late summer for several years. He had also been found clinically sensitive to aspirin, ephedrine and Orthoxine.

His asthma had formerly been accentuated on exposure to barn dusts but this contact had not been present since his retirement at the age of sixty-three. Other precipitating agents were not suspected.

He was studied allergically in 1940 and again in 1949. On both occasions he was found skin-test sensitive to ragweed and gave slightly positive intracutaneous reactions to house dust. However, specific therapy with house dust and ragweed extracts did not significantly change his chronic symptoms. He was found highly sensitive to wheat and rye as a result of experimental feeding tests in 1940, but the avoidance of these foods was only partially effective in controlling his asthma. When re-studied in 1949, all the major allergenic foods were appraised by means of individual food tests;¹¹ he was found highly sensitive to corn, wheat, rye and pork as evidenced by the production of sharp attacks of asthma following these ingestion tests.

This patient was hospitalized in late August during the height of the ragweed

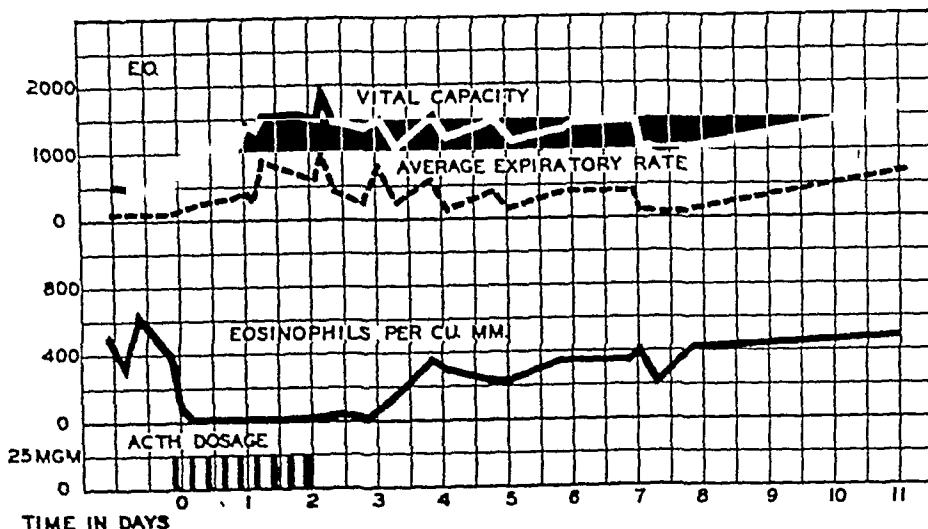


Fig. 3. Variations in the vital capacity, expiratory rate and peripheral blood eosinophils in E.O., a patient with bronchial asthma, following ACTH therapy.

pollinating season, and was treated with 325 mg. of ACTH in divided doses over a period of three days. Sustained improvement in his asthma was noted during the second day of therapy, and symptomatic medications were no longer necessary at the end of the third day. Changes in his ventilatory capacity and eosinophil response are shown in Figure 2. At this time his known allergenic foods were returned to his diet one by one and failed to produce respiratory or other allergic symptoms. He returned home on a general diet, resumed a normal degree of activity for his age and required no symptomatic medications for a period of three weeks.

Upon the recurrence of severe asthma during the fourth week, he was rehospitalized and treated with 225.0 mg. ACTH. Although the pattern of his response was similar to that following his initial course and his improvement persisted for approximately the same duration, there was a detectible clinical difference in the degree of relief in that he had occasional attacks of mild symptoms from which he obtained immediate relief with small doses of epinephrine by inhalation.

Six weeks after this course of therapy and in a state of relapse, he was rehospitalized and treated with Concentrated Adrenal Cortex Extract,¹⁰ and although improved while therapy was maintained, severe asthma recurred three days after stopping treatment.

One week later he received a course of Cortisone therapy; this will be described subsequently.¹¹ Seven days after the cessation of Cortisone and sixteen days following cessation of therapy with cortical extract, he was given a third course of 225.0 mg. ACTH. This was followed by a clinical response comparable in degree and duration to that of the second course of ACTH. It should be emphasized that he has remained on a general diet eating his known food allergens without restrictions since the completion of the initial course of ACTH therapy.

Case 3.—E. O., a woman, aged fifty-five, subject to chronic perennial bronchial asthma and allergic rhinitis since the age of forty-five years, was chosen for this study because of incapacitating asthma which was complicated by a marked degree of pulmonary emphysema. Her continual dyspnea was of such a degree that for several years she had been unable to talk in complete sentences or to walk up a single flight of stairs.

Allergic study in the summer of 1949 revealed an equivocal intradermal reaction

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to house dust, but specific therapy, according to the technique outlined,⁶ failed to change the course of her disabling symptoms. On the performance of individual food tests she developed attacks of acute bronchial asthma following the trial ingestion of rye, potatoes, milk and string beans. However, the specific avoidance of incriminated foods was only partially effective in relieving her symptoms.

Improvement in her asthma and dyspnea was first noted six hours after the initial injection of 25.0 mg. ACTH. After twenty-four hours of therapy this patient was able to talk in full sentences, to walk briskly in the hospital corridors and up a flight of stairs without dyspnea. The repetition of food tests which were formerly associated with the development of acute rhinitis and asthma now failed to produce allergic symptoms. However, aside from these trial tests, she was continued on her restricted diet during and following the initial course of treatment. She remained free of asthma and rhinitis without the need of medications and led a normal life for the following two and one-half weeks. Ventilatory and blood observations are shown in Figure 3.

Thereafter, she showed a gradual recurrence of asthma, and when this reached the former degree of severity she was rehospitalized for a second identical course of ACTH. Although her immediate response was identical to that of the first course, a pronounced weakness developed two days after the cessation of therapy. She was then returned to a general diet with the exception of milk and within a few days her weakness subsided. In other respects her clinical response to this course of ACTH therapy was similar to that of the initial one.

By the time the first course of treatment in the three above cases was completed it became evident that a more extensive study of the effects of ACTH in allergic diseases was indicated. Eight additional asthmatics were studied similarly.

Case 4.—S. H., a man, aged fifty-five years, with a history of intermittent bronchial asthma since the age of ten years, had continuous severe rhinitis and asthma for the past decade. His asthma was complicated by recurrent nasal polypi, aspirin sensitivity and pulmonary emphysema. He received 225 mg. ACTH over a period of forty-eight hours and showed a 75 per cent improvement in his rhinitis and a 50 per cent improvement in his asthma which persisted for only one week. He began using epinephrine by inhalation five days after the cessation of therapy.

Case 5.—B. D., a woman, aged forty-five, with asthma of ten years' duration and known to be clinically sensitive to aspirin, house dust and several major foods had been confined to her bed with incapacitating asthma for the past year prior to starting ACTH therapy. X-ray examination of the chest showed moderate emphysema, residues from previous pleurisy, and obliteration of the right costo-phrenic angle resulting from an old empyema. Her vital capacity doubled following therapy with 225.0 mg. ACTH. This was followed by a clinical response comparable in degree and lie of asthma for a period of two and one-half weeks.

Case 6.—M. H., a woman, aged fifty-six, subject to severe bronchial asthma for twenty years, had been taking 30 grains of aminophylline and eight to ten subcutaneous injections of epinephrine and repeated inhalation of Isuprel daily prior to starting ACTH therapy. She had fractured ribs on several occasions during severe attacks. Her asthma was complicated by moderate pulmonary emphysema and suggestive evidence of pulmonary fibrosis. Her vital capacity also doubled after receiving 225 mg. ACTH. She experienced a marked improvement in her asthma and as-

sociated allergic rhinitis for the following three weeks, during which time aminophylline was not necessary and she was able to reduce materially the use of epinephrine.

Six additional patients with severe bronchial asthma but without pulmonary complications were also treated with Adrenocorticotrophic hormone.

Two patients with seasonal ragweed asthma were relieved of all allergic symptoms for the remainder of the 1949 ragweed pollinating season; their cases will be summarized subsequently.

Case 7.—One male child, R. K., aged ten years, with a history of perennial bronchial asthma of four years' duration and known to be clinically sensitive to house dust, ragweed pollen, fungi and several major foods, received a total dose of 140.0 mg. ACTH over a period of three days. This patient had immediate relief of asthma but had a moderate recurrence of wheezing for two days after returning to his home. He then remained entirely free of asthma for the following month, although in previous years this particular season had been his most troublesome period.

Case 8.—W. E., a man, aged sixty years, subject to perennial allergic rhinitis for ten years and bronchial asthma for one year, had complete relief of allergic symptoms for three weeks after receiving 300 mg. ACTH over a period of three days.

Case 9.—E. U., a man, aged fifty-two, developed perennial nasal allergy at the age of forty-seven which was subsequently complicated by nasal polypi. Within a few hours after his initial polypectomy at the age of forty-eight, he developed severe bronchial asthma which has been present constantly since except for a period of two and one-half months immediately following insulin shock therapy received as treatment for an acute toxic psychosis. An initial course of only 125 mg. ACTH was given because of progressive edema and gain in weight beginning after the fourth dose of 25.0 mg. Although he developed the expected degree of eosinopenia, there was no significant change in the severity of his asthma except for transient improvement during ACTH administration.

A second course of the same amount given three weeks later was followed by moderate improvement during the period of administration which persisted only for a four-day period. A comparable gain in weight and clinical edema again developed which prompted us to discontinue therapy.

A third course two weeks later, consisting of 50 mg. daily in divided doses for three days, failed to produce edema or to cause any improvement in his asthma. Subsequently, this patient was diagnosed specifically and found sensitive to milk. The removal of milk and wheat from his diet has been more effective in controlling his asthma than ACTH administration in the dosage schedules employed. Although the cumulative addition of wheat was tolerated, each attempt to reintroduce milk has resulted in acute abdominal cramps and diarrhea.

Case 10.—J. S., aged fifty-eight, and previously reported by Markson,³ had been subject to rheumatoid arthritis for twelve years and mild perennial bronchial asthma for one year prior to starting ACTH therapy June 20, 1949. He has received a daily dosage of ACTH sufficient to control his rheumatoid arthritis since. While he was treated for his arthritis, we noted a gradual improvement in his asthma during the first twelve days of therapy; this was based on clinical evidence as well as a change in his expiratory rate from 800 to 1,700 c.c. per second.

Although undiagnosed and untreated from the allergic standpoint, he continued without troublesome asthma since this time, except for periods beginning four months

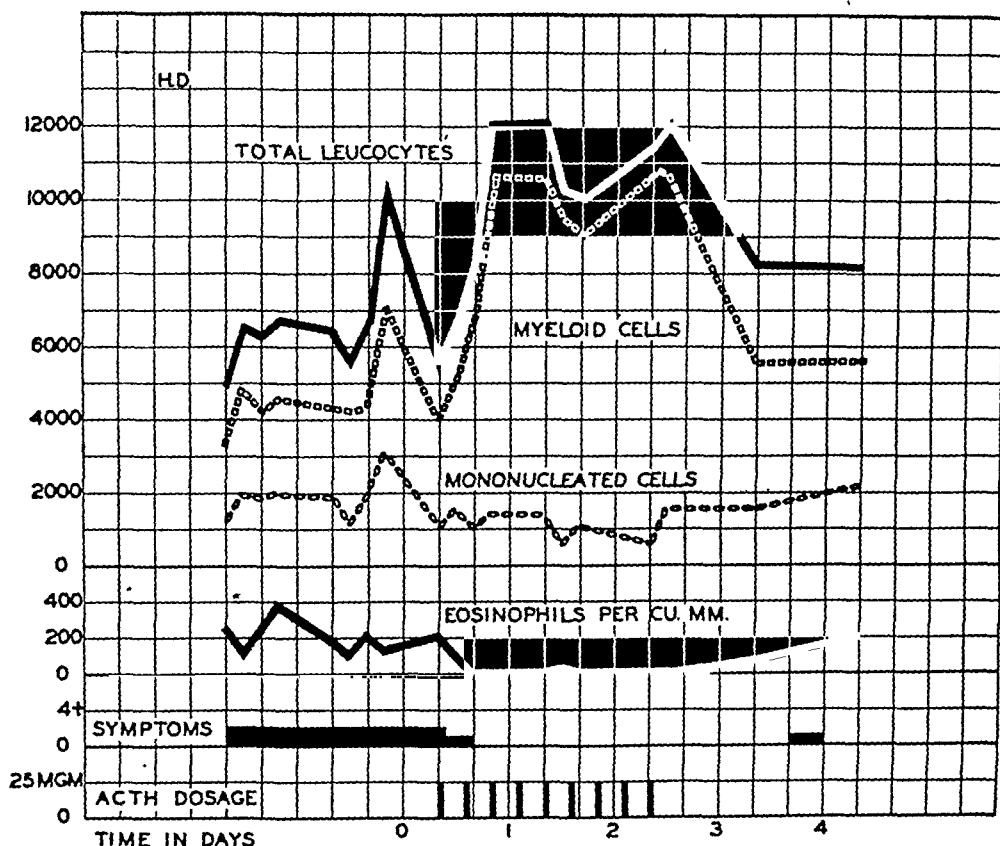


Fig. 4. Variations in the cellular elements of the peripheral blood as determined by glycol-stain counting chamber differential technique and the symptom response in H.D., a patient with ragweed hay fever, following ACTH therapy.

after the institution of therapy when attempts were made to reduce the amount of ACTH to a minimum dose capable of relieving his arthritic pain. During these periods when receiving 12.5 mg. ACTH daily, his asthma recurred in its former severity.

Three patients with acute ragweed hay fever were hospitalized between the dates of August 30 and September 5, 1949; they were placed in corner rooms with open windows. The ragweed pollen count remained over 300 per day throughout the period during which the following observations were made.

The number of times per twenty-four hours that each patient sneezed, sniffled, coughed or blew her nose was recorded for forty-eight hours prior to, during the course of and for four days following the completion of ACTH therapy. Eosinophil, total leukocyte, myeloid and mononucleated cells were determined by the method previously described. Pre- and post-treatment skin tests, skin biopsies and passive transfer studies were made; these will be reported in a subsequent article.

Case 11.—H. D., a woman, aged fifty, had been subject to yearly hay fever from mid-August to the second week of October since 1944. She had received preseasional specific therapy since the onset of her ragweed symptoms. She also had been subject to typical rheumatoid arthritis of twelve years' duration.

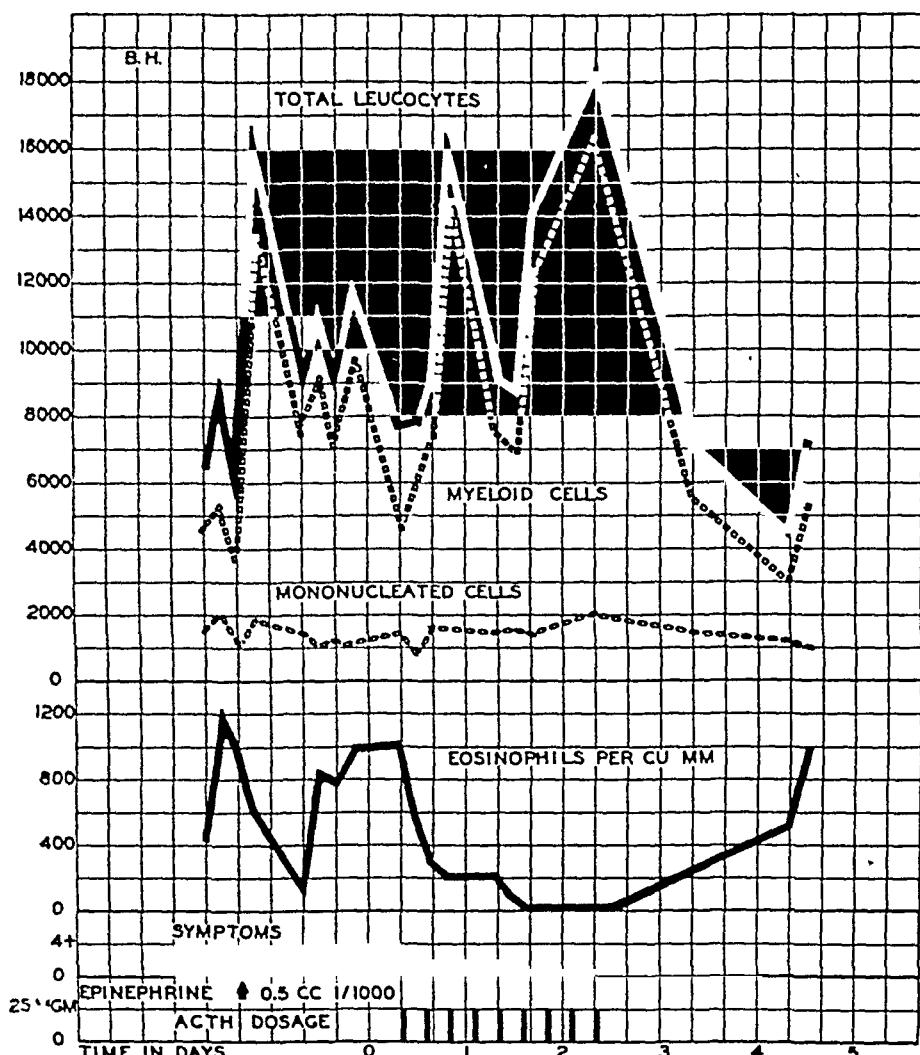


Fig. 5. Variations in the cellular elements of the peripheral blood as determined by glycol-stain counting chamber differential technique and the symptom response in B.H., a patient with ragweed hay fever and bronchial asthma, following ACTH therapy.

She received 225 mg. ACTH in divided doses over a period of forty-eight hours. Evidence of improvement in her nasal symptoms, first noticed thirty minutes following the initial injection of 25.0 mg., progressed to complete relief of hay fever at the end of six hours. Aside from mild sneezing in the afternoon of the third day, she had no further hay fever throughout the remainder of the ragweed hay fever season. Her arthritic symptoms also improved but recurred ten days after the cessation of ACTH therapy. Variations of the blood elements and a summary of the clinical data are shown in Figure 4.

Case 12.—B. H., a woman, aged thirty-eight, had been subject to perennial nasal allergy with superimposed severe ragweed hay fever for the past sixteen years, complicated by seasonal bronchial asthma for the past twelve years. As may be noted in Figure 5, she developed leukocytosis and eosinopenia immediately after an

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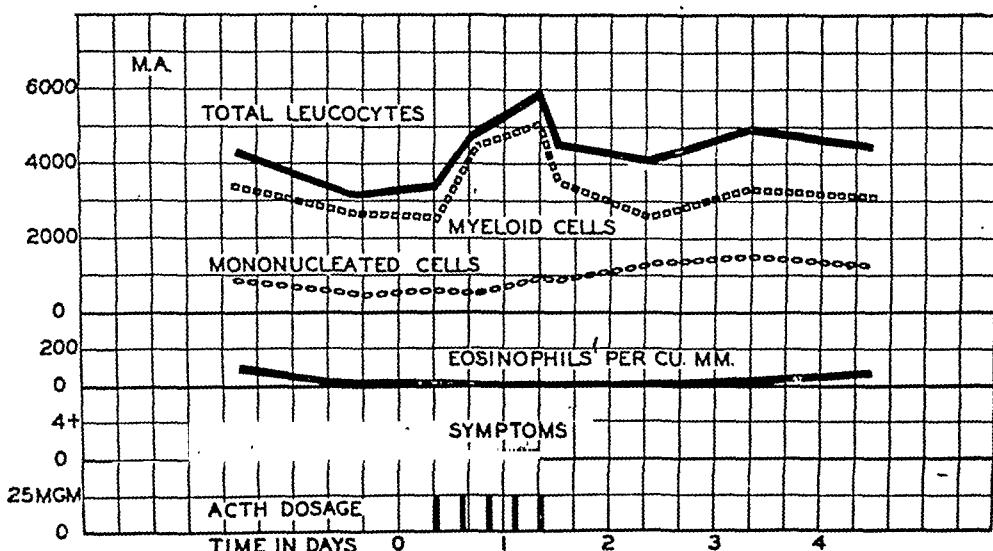


Fig. 6. Variations in the cellular elements of the peripheral blood as determined by glycol-stain counting chamber differential technique and the symptom response in M.A., a patient with allergic headache, ragweed hay fever and bronchial asthma, following ACTH therapy.

injection of 0.5 c.c. epinephrine which had been given in order to control severe asthma developing immediately following skin testing with ragweed extract.

She received 225 mg. of ACTH during a period of forty-eight hours. Her respiratory symptoms began to improve thirty minutes after the first dose of 25.0 mg. and were completely relieved at the end of forty-eight hours. Repetition of the skin tests at this time failed to produce any symptoms. She had no further hay fever or asthma for the remainder of the pollen season, and her perennial rhinitis remained 50 per cent improved for the following four months compared with the severity of her symptoms during a comparable period in previous years.

Case 13.—M. A., physician's wife, aged thirty-seven, had been subject to perennial rhinitis and severe incapacitating headaches since childhood. These symptoms had been relieved for a period of two years as a result of dust therapy and the avoidance of several major allergenic foods. An intractable cough which began in April, 1949, was controlled by the additional avoidance of beet and cane sugar. In each instance, individual food tests with cane sugar and with beet sugar were followed in ten minutes by the onset of violent coughing. Similarly, the accidental or inadvertent ingestion of either type of sugar had been followed by the precipitation of coughing.

Her initial ragweed hay fever and bronchial asthma developed while on a motor trip at the height of the 1949 pollen season, necessitating her return to the hospital September 5, 1949. During the twenty-four-hour period prior to ACTH therapy she sneezed, sniffled, coughed or blew her nose 640 times. She was maintained on her formerly restricted diet during the course of administration of 125 mg. ACTH. A decrease in the incidence and severity of sneezing occurred forty minutes after the initial intramuscular injection of 25.0 mg.

Fifteen minutes after each injection of 25.0 mg. ACTH this patient experienced a transient vasoconstriction with pallor and coldness of her extremities but without a significant change in her blood pressure. These manifestations were attributed to the small quantity of posterior pituitary fraction present in this material. Three hours after the initial injection she complained of bilateral deep pelvic pain which radiated caudally and anteriorly into the groin. She remarked that this pain was identical in character to premenstrual pain present prior to surgical removal of the left ovary and x-ray castration of the right ovary four and three years previously.

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respectively. As additional treatment was given every six hours, these continued with sufficient intensity to require the use of opiates for relief. Since we felt that an adequate therapeutic response had been obtained and that these symptoms might represent an overdose phenomenon, her ACTH therapy was discontinued after five intramuscular injections totalling 125.0 mg. These pelvic symptoms persisted for a week after the cessation of treatment.

Forty-eight hours after the completion of ACTH therapy, her beet and cane individual food tests were repeated but failed to produce symptoms. She was then returned to a general unrestricted diet. With the exception of estrogen therapy which was begun following castration, discontinued during ACTH therapy and restarted 5 days after stopping ACTH, she received no other type of medication.

Following massive dust exposure in January, 1950, at the height of the house dust season,¹² she developed a recurrence of coughing, asthma, headache and generalized edema with a gain in weight of 15 pounds. These symptoms were promptly relieved following a second course of 225 mg. ACTH. This patient showed a progressive weight loss coincident with a marked diuresis during the first five days after the onset of ACTH therapy. During the second day of therapy she had a recurrence of her formerly described pelvic pain for the first time since her previous course of ACTH. Although she has again had complete relief of her allergic symptoms, this pain has persisted up to the present time, that is, two weeks after treatment with ACTH.

DISCUSSION

With the exception of the two cases of seasonal ragweed asthma, the other asthmatics selected for this study of the effectiveness of adrenocorticotropic hormone in bronchial asthma were perennial advanced cases of this disease. As judged from the age of the onset of asthma, the majority of these patients would qualify for the designation of "intrinsic asthma" as described by Rackemann.¹ Furthermore, several of the cases were complicated by nasal polypi and aspirin sensitivity, a combination which has been striking in respect to the difficulty in the management of bronchial asthma from the standpoint of specific allergic diagnosis and therapy. It should be re-emphasized that the patients chosen for the administration of ACTH were not a random sample of bronchial asthma but represented the most difficult diagnostic and therapeutic problems gleaned from a private practice of allergy.

Ten of the eleven asthmatics to whom a short course of ACTH had been administered obtained a marked degree of relief of their chronic symptoms. The duration of relief varied from a week to as long as five months following a single course of therapy, ranging in total dosage of ACTH from 125.0 to 325.0 mg. One case, E. U., developed evidence of fluid retention early in the course of each of two attempts to treat him with ACTH in a manner found effective in the other asthmatics. Although he failed to develop edema in the third course of ACTH at a lower dosage level, he also failed to show a significant degree of improvement in his allergic symptoms when treated for a period of time found to be effective in other cases.

We have had the opportunity of observing only one patient, J. S.,³ treated with continuous ACTH therapy. This arthritic patient with mild

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complicating bronchial asthma has received a dosage varying from 12.0 to 75.0 mg. daily for the past eight months. As previously stated, his asthma recurred when treated for several days at the lower level of dosage although he remained free of arthritic pain. With a further reduction in dosage his arthritic pain also recurred.

In general, prolonged continuous therapy for the treatment of bronchial asthma does not seem to be indicated in view of the response obtained from short intermittent courses of therapy.

The degree of relief of asthma in the ten cases showing a favorable response varied from complete to approximately 50 per cent. By complete relief is meant an absence of rhonchi as detected on repeated chest examinations, the maintenance of normal vital capacities in respect to the individual's surface area and the ability to lead normal lives without obvious wheezing in the absence of taking medications for the relief of asthmatic symptoms. In general, the most striking results were obtained in those cases uncomplicated by other pulmonary pathology. ACTH was least effective in the asthmatics shown by x-ray and clinical evidence to have pulmonary emphysema, extensive scarring resulting from pleurisy and empyema. Our experience has shown that in most instances the greater the degree of pulmonary emphysema the less satisfactory was the clinical response to ACTH administration. The outstanding exception to this statement is the case of E. O.

Not only is adrenocorticotrophic hormone effective in relieving temporarily the symptoms of severe, long sustained bronchial asthma, but it also changes the reactivity of allergic individuals known to be specifically sensitized to food and inhalant allergens. In several instances foods known to produce acute accentuations in bronchial asthma prior to the administration of ACTH were tolerated without evidence of symptoms during the course of and for a period of time following ACTH therapy. Similarly, test procedures with house dust and ragweed pollen which produced constitutional reactions prior to therapy failed to do so during or immediately following treatment with adrenocorticotrophic hormone. It should be emphasized, however, that ACTH seems capable of producing only a transient refractoriness to known allergenic offenders.

With the recurrence of bronchial asthma following a course of ACTH therapy, symptoms are readily relieved following the inhalation of a small amount of epinephrine spray. This is in decided contrast to the ability of epinephrine to relieve symptoms of similar severity prior to the administration of ACTH. Whereas an individual might have found it necessary to inhale 1:100 epinephrine eight to ten times prior to hormone therapy to obtain relief from an attack of asthma, literally a "whiff" of the 1:100 concentration effects prompt relief of asthma of comparable severity after ACTH therapy. This change in the effectiveness of epinephrine is only temporary.

ACTH appears to be a remarkably effective agent in bringing about com-

plete relief of ragweed hay fever as evidenced by the striking results in three patients treated during the height of the 1949 ragweed hay fever season. Not only did this therapy eradicate all evidences of clinical hay fever but protected the three individuals so treated for the remainder of the current ragweed pollinating season. The effect on the skin tests and passive transfers of these patients to ragweed pollen extracts will be presented in another publication.¹⁰

In addition to the relief of asthma and rhinitis as a result of ACTH treatment, these patients usually experienced marked general improvement, in that they noted an increased warmth of their extremities, an apparent increased vascularity of the nail beds and skin; they claimed to feel less tense and apprehensive, more relaxed and tranquil. That improvement in these symptoms as well as the asthma was not due to suggestion is attested by the fact that in many instances the patients were unaware of the exact time at which ACTH therapy started, placebos containing a small amount of propylene glycol in saline having been administered intramuscularly for several doses prior to the administration of ACTH with the patient understanding that he was receiving potent preparations. In no instance did evidence of clinical improvement occur under such circumstances.

Variations in the blood elements following ACTH therapy has been discussed in previous publications.^{7,12} In general, these consist of an initial decrease in the total leukocyte count, followed by a leukocytosis and eosinopenia.

We have not observed any deleterious effects from ACTH in allergic individuals treated with short-term intermittent courses of therapy as outlined in this communication. Neither has there been any unpleasant side effects with the exception of the so-called pelvic cramps in the case of M. A. We wonder if these symptoms may have been the result of stretching of the adrenal capsule as a consequence of transient enlargement of the gland, or possibly as the result of hemorrhages in the adrenal cortex.

In our experience in treating allergic individuals with ACTH, we have learned to watch for the following course of sequential events: The dosage of ACTH is started at 25.0 mg. intramuscularly every six hours with the aim of obtaining a prompt and maximum glandular stimulation of short duration. It is continued at this level even though the eosinophils markedly diminish or disappear from the peripheral blood; this usually occurs within twenty-four hours from the time of the first dose. We observe the patient's fluid intake and output as well as the daily weight for, as a rule, the dosage is reduced 50 per cent in the event of a definite oliguria or a gain in weight of 2 to 3 pounds in twenty-four hours. Most adult patients and some children, particularly those with eczema, tolerate ACTH therapy at a dosage of 25.0 mg. every six hours for a total of nine doses without hazard even though there is no deliberate attempt made to regulate the electrolyte balance.

It should be emphasized, finally, that dangers said to be associated with

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ACTH therapy pertain to long-continued treatment and thus far in our experience have not been observed in therapy consisting of short intensive courses followed by relatively long rest periods as employed in this study.

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CORRECTION

In the volume *Allergy in Relation to Otolaryngology* by French K. Hansel, M.D., F.A.C.A., published recently by The American College of Allergists, the question on page 72 was wrongly attributed to Kenneth L. Craft, M.D. The correct name is Bennett Craft, M.D., F.A.C.A., Indianapolis, Indiana.

ADRENOCORTICOTROPIC HORMONE (ACTH)

Gross and Histologic Effects on Skin Tests and Passive Transfer

MICHAEL ZELLER, M.D., F.A.C.A.,

THERON G. RANDOLPH, M.D., F.A.C.A., and JOHN P. ROLLINS, M.D.

Chicago, Illinois

DURING the course of therapy of various allergic states with adrenocorticotrophic hormone, it was considered that a study of skin responses might elucidate to some extent the action of the drug. Patients with hay fever were selected for the study because of the constancy of skin responses as related to clinical symptoms.

Histologic studies of the allergic wheal reported by Berger and Lang,^{2,3} and Kline, Cohen and Rudolph⁴ reveal that eosinophilia in the inflammatory exudate is the most constant finding. The latter authors state that twenty to thirty minutes after the injection of the allergen there was pronounced inflammation with the majority of the wandering cells consisting of eosinophils.

In the light of these findings our own histologic studies were done twenty to fifty-five minutes after the injection of allergen. Serial biopsies were not possible, for the study was limited to two patients because of scarcity of the drug.

PROCEDURE

Two patients, H. D. and B. H., with ragweed hay fever were admitted to the hospital August 30, 1949. Scratch tests with thirty-six common pollens and animal danders were done and recorded. Intradermal serial dilutions of ragweed were applied to the arm and the reactions noted. Two hours later .02 c.c. of 1:500 ragweed solution was injected intradermally in the left lower abdominal quadrant. Twenty-five minutes after injection of the ragweed a diamond-shaped area 5 cm. from the wheal was infiltrated with two per cent procaine. A biopsy of the skin including the wheal and surrounding erythema was then taken. One of the patients, B. H., developed a generalized reaction with asthma and urticaria necessitating four minims subcutaneous epinephrine prior to completion of the biopsy.

Passive transfer was done by injecting intradermally .15 c.c. blood serum of subject H.D. into the right and left lower abdominal quadrants of ragweed non-sensitive recipient P and into left lower abdominal quadrant of recipient R. The serum of subject B.H. was similarly injected into ragweed non-sensitive recipient Z. Twenty-four hours later a skin biopsy of the sensitized site, using the technique already described, was taken from recipient P without ragweed injection. Recipients R and Z were injected

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The adrenocorticotrophic hormone (ACTH) was supplied by Armour and Company through the courtesy of Dr. John R. Mote.

The histologic studies were made by Dr. H. Ivan Brown, pathologist of the Ravenswood Hospital, Chicago, Ill.

with .02 c.c. of the 1:500 ragweed extract at the sensitized sites, following which a wheal with pseudopods 2 cm. in diameter developed in recipient R and 4 by 5 cm. in recipient Z. Skin biopsies including the wheals with surrounding erythema were taken thirty minutes after ragweed injection in recipient R and fifty minutes after ragweed injection in recipient Z. Control ragweed injections produced circular whealing measuring 4 mm. with surrounding erythema of 2 mm. Forty-eight hours after passive transfer a second skin biopsy was taken from recipient P thirty-five minutes after injection of .02 c.c. of 1:500 ragweed extract into the remaining sensitized area in the right lower abdominal quadrant.

Treatment of the two hay fever patients with adrenocorticotrophic hormone (ACTH) was started at 9:00 a.m., September 2, 1949, and stopped at 9:00 a.m., September 4, 1949, when the number of eosinophils per cu. mm. of blood were zero in subject H.D. and 56 in subject B.H. At 9:30 a.m. scratch tests and serial intradermal ragweed extract were applied to both hay fever subjects and recorded as prior to adrenocorticotrophic hormone therapy. At 11:00 a.m. of September 4, 1949, .02 c.c. of 1:500 ragweed extract was injected intradermally into the right lower abdominal quadrant of hay fever subjects H.D. and B.H. Thirty and fifty-five minutes later, after whealing, skin biopsy was performed as before. At 4 p.m. September 4, 1949, .15 c.c. of post-ACTH treatment serum of subject H.D. was injected intradermally into the right lower abdominal quadrant of recipient R. The post-ACTH treatment serum of subject B.H. was similarly injected into recipient Z.

Forty-eight hours after passive transfer with post-ACTH treatment serum, .02 c.c. of 1:500 ragweed extract was injected intradermally into the sensitized areas of recipients R and Z. Skin biopsies were again taken as described with pre-ACTH treatment serum. Control ragweed injections into non-sensitized areas produced reactions similar to the previous controls.

The skin specimens were then prepared in the routine manner and stained with hematoxylin and eosin.

Three ragweed sensitive patients, H.D., B.H., and M.N., were skin tested in the left side of the back with scratch and intradermal ragweed extract, histamine and ACTH. The ACTH in this study consisted of 25 mg. dissolved in 2 c.c. of normal saline solution. The histamine solution contained 1 mg. of histamine phosphate per c.c. (a 1:1000 solution), equivalent to 0.36 mg. of histamine base. The intradermal ragweed solution consisted of 1:500 dilution, and for the scratch test the concentrated ragweed extract was used. Thirty minutes later mixtures of $\frac{2}{3}$ ACTH solution and $\frac{1}{3}$ each of ragweed and histamine were applied on the right side of the back by the scratch and intradermal methods as in the controls. Two hours later ragweed hay fever subjects H.D., B.H. and M.N. were scratch tested with ragweed extract on the right forearm at three sites 3 cm. apart, and the usual whealing and erythema was noted. Twenty minutes later ACTH was

TABLE I. THE WHEALING RESPONSE OF RAGWEED AND HISTAMINE WITH ADRENOCORTICOTROPIC HORMONE ACTH, IN 3 HAY FEVER PATIENTS

Subjects	Materials	Scratch Tests	Intradermal Tests
H.D. B.H. and M.N.	Mixture of: Ragweed, one third ACTH, two thirds	Wheal and Erythema	Wheal and Erythema
	Ragweed control	Wheal and Erythema	Wheal and Erythema
	ACTH control	No reaction	Small circular wheal with erythema
	Mixture of: Histamine, one third ACTH, two thirds	Wheal and Erythema	Wheal and Erythema
	Histamine control	Wheal and Erythema	Wheal and Erythema

TABLE II. THE WHEALING RESPONSE OF RAGWEED SCRATCH TESTS IN SITES PRETREATED 10 MINUTES EARLIER WITH ADRENOCORTICOTROPIC HORMONE, ACTH

Subjects	Materials	Scratch Tests
H.D. B.H. and M.N.	ACTH applied to scratch site. Concentrated ragweed extract applied 10 minutes later	Wheal and erythema
	ACTH control applied to scratch site. Concentrated ragweed extract control applied to scratch site	No reaction
		Wheal and erythema

first applied to scratch tests on the left forearm, ten minutes after which ragweed was applied at the same site.

RESULTS

Skin Tests.—The thirty-six inhalant extracts applied to the back of the hay fever subjects H.D. and B.H. revealed numerous reactions varying from zero to four plus. The ragweed reactions exemplified the latter degree of reaction. Serial ragweed dilutions from 1:500 to 1:62,500 applied intradermally on the arm likewise revealed whealing and erythema starting from four plus and diminishing in proportion to strength of solution. After treatment with adrenocorticotrophic hormone repeat test studies were essentially the same.

The results of the studies shown in Table I clearly indicate that $\frac{2}{3}$ adrenocorticotrophic hormone mixed with $\frac{1}{3}$ ragweed and histamine and applied by scratch and intradermal methods failed to alter the response obtained by ragweed and histamine alone.

In Table II it is shown that the application of adrenocorticotrophic hormone to scratch tests followed ten minutes later by ragweed concentrate produces whealing the same as ragweed controls.

Histopathologic Studies.—Tables III and IV. The biopsies taken from the hay fever subjects prior to ACTH therapy reveal eosinophilic infiltration and edema as constant and prominent features. After ACTH therapy the biopsies show absence of eosinophils in one subject and sharp reduction of eosinophils in the other. There is in addition marked increase of polymorphonuclear cells with a decrease of monocytes and lymphocytes.

The sections taken from the passive transfer sites also disclose edema and eosinophilic infiltration, but there is no significant change in the pro-

TABLE III. HISTOLOGIC STUDIES OF SKIN TESTS AND PASSIVE TRANSFERS WITH ADRENOCORTICOTROPIC HORMONE ACTH, IN RAGWEED HAY FEVER, SEPTEMBER, 1949
PRIOR TO TREATMENT WITH ACTH

Subject	Eosinophils Per Cu. MM. of Blood	Subcutaneous Tissue	Corium	Conclusions
Hay Fever H.D.	220 or 3.3 per cent	No tissue in section	Moderate perivascular reaction and edema. Differential in per cent Eos. 25 Polys. 50 Monos. & Lymphs. 25	Allergic Reaction
Hay Fever B.H.	781 or 8.8 per cent	Few vessels. Inflammatory reaction minimal with 10 to 15 cells about each capillary. Differential in per cent	Marked acute inflammatory reaction and edema about all vessels. Differential in per cent Eos. 15 Polys. 75 Monos. & Lymphs. 10	Moderate Allergic Reaction
Passive Transfer Recipient R.	111 or 1.2 per cent	Diffuse inflammatory reaction and edema, particularly about all small capillaries. Differential in per cent	Perivascular inflammatory reaction and edema prominent. Differential in per cent Eos. 45 Polys. 35 Monos. & Lymphs. 20	Severe Allergic Reaction
Passive Transfer Recipient Z.	143 or 1.5 per cent	Slight inflammatory reaction about small capillaries. Moderate edema. Differential in per cent	Moderate inflammatory reaction particularly about small capillaries. Edema prominent. Differential in per cent Eos. 15 Polys. 55 Monos. & Lymphs. 30	Moderate Allergic Reaction

portion or type of cellular infiltration as a result of adrenocorticotrophic hormone therapy.

In one recipient biopsy of the serum alone without antigen revealed moderate reaction in the corium with 80 per cent lymphocytes and monocytes and 20 per cent polymorphonuclear cells (Table V). The subcutaneous tissue was normal and the reaction was considered as nonspecific. The sections after ragweed injection revealed the type of reaction observed in the other passive transfer recipients but to a lesser degree.

DISCUSSION AND SUMMARY

It seems clear that scratch and intradermal tests on ragweed sensitive patients are not altered after adequate ACTH therapy for clinical relief. It is evident also that gross and histologic studies of passive transfer sites likewise are not influenced by ACTH therapy. Histologic studies of passive transfer sites produced with pre- and post-ACTH treatment serum reveal characteristic edema and eosinophilic infiltration. There is, however, a sharp contrast in the treated hay fever subject who presents a striking diminution of eosinophils in ragweed wheals in parallel with the blood. Using the technique of one of us² quantitative blood eosinophil determination per cubic millimeter prior to ACTH therapy varied from 1265 to 781 in one subject and from 396 to 88 in the other. After treatment

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TABLE IV. HISTOLOGIC STUDIES OF SKIN TESTIS AND PASSIVE TRANSFERS WITH
ADRENOCORTICOTROPIC HORMONE ACTH, IN RAGWEED HAY FEVER,
SEPTEMBER, 1949
AFTER TREATMENT WITH ACTH

Subjects	Eosinophils per cu. mm. of blood	Subcutaneous Tissue	Corium	Conclusions
Hay Fever H.D.	0	Moderate inflammatory reaction limited to capillary walls	Marked acute inflammation and edema. Vessel walls studded with polys.	Nonspecific Inflammatory Reaction
		Differential in per cent Eos. 0 Polys. 05 Monos. & Lymphs. 5	Differential in per cent Eos. 1 Polys. 89 Monos. & Lymphs. 10	
Hay Fever B.H.	55 or 0.21 Per cent	Slight perivascular infiltration. Moderate edema.	Moderate perivascular inflammation and edema	Slight Allergic Reaction in Corium only.
		Differential in per cent Eos. 0 Polys. 90 Monos. & Lymphs. 10	Differential in per cent Eos. 5 Polys. 65 Monos. & Lymphs. 30	
Passive Transfer Recipient R.	Not Done	Diffuse inflammatory reaction and edema, particularly about all small capillaries	Marked perivascular inflammatory reaction and edema.	Severe Allergic Reaction.
		Differential in per cent Eos. 35 Polys. 40 Monos. & Lymphs. 25	Differential in per cent Eos. 5 Polys. 25 Monos. & Lymphs. 70	
Passive Transfer Recipient Z	1	Slight inflammatory reaction about small capillaries. Moderate edema	Moderate inflammatory reaction, particularly about small capillaries Edema prominent	Moderate Allergic Reaction.
		Differential in per cent Eos. 15 Polys. 60 Monos. & Lymphs. 25	Differential in per cent Eos. 2 Polys. 68 Monos. & Lymphs. 30	

TABLE V. CONTROL HISTOLOGIC STUDIES OF PASSIVE TRANSFER IN THE ABSENCE OF ADRENOCORTICOTROPIC HORMONE ACTH

Subject	Site Prepared for Passive Transfer But Without Addition of Antigen	Site Prepared for Passive Transfer With Addition of Intradermal Ragweed
Passive Transfer Recipient P.	Subcutaneous tissue normal	Subcutaneous tissue shows scattered inflammatory cells in small numbers Differential in per cent Eos. 8 Polys. 50 Monos. & Lymphs. 42
	Corium shows slight edema and perivascular exudation Differential in per cent Eos. 0 Polys. 20 Monos. & Lymphs. 80	Corium shows moderate edema and increased vascularity and exudate Differential in per cent Eos. 5 Polys. 8 Monos. & Lymphs. 87

with ACTH, blood eosinophils rapidly diminished to 56 in the first and to zero in the second. Histologic studies of ragweed wheals taken at this time disclosed few or no eosinophils in the first subject and diminution of eosinophils in the second subject in contrast to profuse tissue eosinophilia prior to therapy. In addition the polymorphonuclear cells increase and the lymphocytes decrease. This indicates that adrenocorticotropic hormone in the doses employed materially reduces or inhibits blood and tissue eosinophils in the treated patient. The inhibiting factor is either not transmitted to passive transfer recipients or if so in quantities insufficient to be

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TABLE VI. HISTOLOGIC STUDIES OF RAGWEED WHEAL BEFORE AND AFTER ADMINISTRATION OF EPINEPHRINE

Subject	Method	Subcutaneous Tissue	Corium
Hay Fever S.H.	Control intradermal injection of ragweed.	Minimal inflammation. Marked edema. Differential in per cent Eos. 15 Polys. 75 Monos. & Lymphs. 10	Marked acute inflammatory reaction and edema about all vessels. Differential in per cent Eos. 10 Polys. 70 Monos. & Lymphs. 20
	Ragweed wheal on abdomen, excised 20 min. after injection of epinephrine in arm.		Moderate perivascular round cell infiltration. Differential in per cent Eos. 0 Polys. 10 Monos. & Lymphs. 90

detected by this technique. In one hay fever subject a biopsy of a ragweed wheal taken before ACTH therapy also revealed complete absence of eosinophils following the hypodermic injection of five and two minimis of epinephrine given at fifteen-minute intervals respectively. (Table VI.)

Numerous observers^{1,4,5,8,9} have demonstrated that histamine antagonists such as Pyribenzamine and Benedryl inhibit allergic wheals when administered orally or locally by application before antigen or as an admixture with antigen. Adrenocorticotrophic hormone applied locally in like manner fails to demonstrate such inhibiting action on the ragweed or histamine wheal. Yet, at the same time adrenocorticotrophic hormone therapy effects rapid and complete relief of clinical ragweed hay fever and asthma. This suggests altering of the hypersensitivity state of the clinical shock organ without influencing gross skin effects. The histamine antagonists on the other hand modify not only the shock organ in relieving hay fever but alter skin responses as well. This indicates dissimilarity in the mode of action of the two types of drugs, the cause of which is as yet unknown.

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CONCENTRATED ADRENAL CORTEX EXTRACT Its Effect in Bronchial Asthma and Gastrointestinal Allergy

THERON G. RANDOLPH, M.D., F.A.C.A.

and

JOHN P. ROLLINS, M.D.

Chicago, Illinois

THE favorable effects of adrenocorticotropic hormone (ACTH-Armour) and Cortisone (Compound E-Merck) on rheumatoid arthritis^{5,6} and the effects of ACTH on other allergic conditions reported at the recent ACTH Conference (October 21-22, 1949),^{2,3,6,12} and subsequently,^{1,3} prompted the use of adrenal cortical extract in bronchial asthma and other allergic syndromes. Consequently, Concentrated Adrenal Cortex Extract in Propylene Glycol*, containing 250 glycogen deposition units per c.c., which are equivalent to 25 mg. of Compound S and 50 mg. Compound E, as determined by biological assay, was used in the following study.

Three patients, including two asthmatics (C. P. and A. S.) and one case of gastrointestinal allergy (M.S.) who had previously responded favorably to one or more courses of ACTH and subsequently had been reported,¹⁰ and one case of bronchial asthma (P. A.) who had not previously received endocrine therapy were selected for this study.

Each of the three asthmatics, who had been subject to severe perennial bronchial asthma and were refractory to conventional allergic management including prolonged periods of hospitalization, were hospitalized; and the following determinations were made during a period of forty-eight hours prior to, during the interval of administration of Concentrated Adrenal Cortex Extract, and for several days thereafter: (1) The average of three maximum expirations was taken as the vital capacity, charted by the upper solid line in Figures 1, 2 and 3. (2) The time required to exhale an arbitrarily selected volume of air, the amount being chosen in relation to the patient's vital capacity and measured in terms of the cubic centimeters of air expired per second, was designated the expiratory rate. This technique was modified after that originally described by Hamburger.^{4,11} The expiratory rate is plotted in the figures as the second or broken line. (3) The absolute number of circulating eosinophils per cubic millimeter of blood was determined by employing the direct counting chamber glycol stain technique previously described by one of us;⁷ it is shown graphically by the lower solid line in Figures 1, 2, 3, and 4. (4) All epinephrine was discontinued for twenty-four hours immediately prior to the administration of Concentrated Adrenal Cortex Extract, and aminophylline was administered as necessary for the relief of severe asthma.

Similar blood studies were made in the single case of gastrointestinal

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allergy. The total leukocyte count was plotted in the upper solid line; the myeloid, mononucleated and eosinophil cells were plotted in the successive lines of Figure 4.

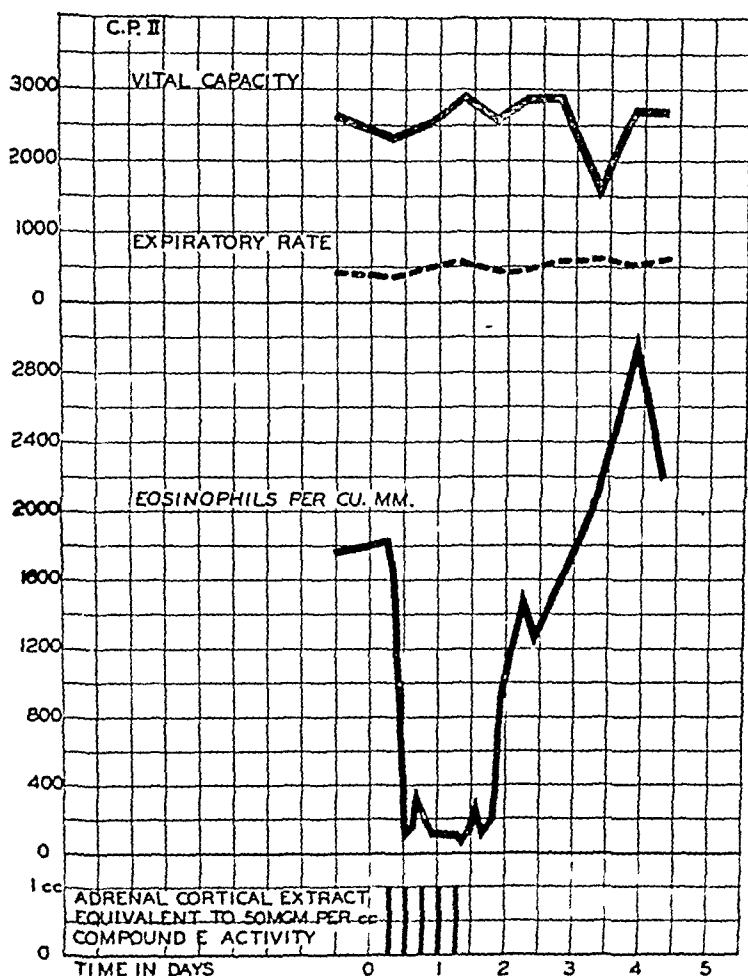


Fig. 1. Variations in the vital capacity, expiratory rate and peripheral blood eosinophils in C. P., a patient with bronchial asthma, following treatment with Concentrated Adrenal Cortex Extract.

Case 1.—C. P., a man, aged forty-three years, subject to incapacitating bronchial asthma of seven years' duration, complicated by allergic rhinitis, nasal polypi and chronic sinus infection, was hospitalized in September, 1949, for ACTH therapy. He received 225.0 mg. ACTH in divided doses over a forty-eight-hour period. His pre-treatment vital capacity of 2,850 c.c. of air and his expiratory rate of 500 c.c. of air per second prior to treatment changed to 4,860 c.c. vital capacity and an expiratory rate of 4,500 c.c. per second following this therapy, coincident with relief of his asthma and other allergic symptoms. At the end of the first twenty-four hours of therapy he was not only free of asthma but his sense of smell returned for the first time in many months, and he was able to breath normally through his nose. He remained without troublesome allergic symptoms for the following three weeks, after which he had a gradual return of rhinitis and asthma. He was rehospitalized in October, 1949, with an initial vital capacity of 1,800 c.c. of air and an expiratory rate of 310 c.c. of air per second. After an identical course of ACTH therapy, he again had almost complete relief of allergic symptoms, having a vital capacity of 4,850 c.c. of

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air and an expiratory rate of 3,800 c.c. of air per second. This degree of improvement persisted for a two-and-one-half-week period.

Upon the recurrence of asthma of the former degree of severity, he was rehospitalized in October for a course of Concentrated Adrenal Cortex Extract. He re-

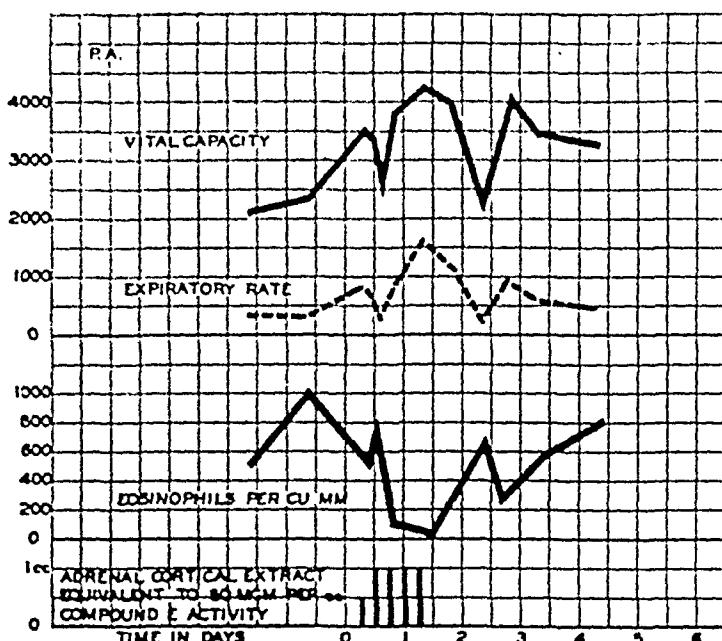


Fig. 2. Variations in the vital capacity, expiratory rate and peripheral blood eosinophils in P. A., a patient with bronchial asthma, following treatment with Concentrated Adrenal Cortex Extract.

ceived five intramuscular doses of 1.0 c.c. each of this material. Although there was a prompt fall in the level of the peripheral blood eosinophils, there was no significant change either in his vital capacity or expiratory rate as shown in Figure 1. Neither was there a change in the severity of his rhinitis or asthma.

It has subsequently been shown that he was not refractory to hormone therapy inasmuch as he has since responded on two different occasions to ACTH therapy in a similar manner as he had done prior to treatment with adrenal cortex extract. This response has been described in more detail elsewhere.⁸

Case 2.—P. A., a man, aged fifty-five years, had been subject to incapacitating bronchial asthma for the past seven years and had failed to respond to conventional allergic diagnosis and therapy. For a period of three weeks prior to starting treatment with Concentrated Adrenal Cortex Extract he had been hospitalized for status asthmaticus and treated unsuccessfully by means of the usual symptomatic measures; these included large and frequent doses of epinephrine, aminophylline and various antihistaminics as well as various trial elimination diets. He received an initial dose of 0.5 c.c. and five subsequent doses of 1.0 c.c. of Concentrated Adrenal Extract intramuscularly over a period of two days. There was a transient improvement in his vital capacity and expiratory rate beginning twelve hours after the initial dose of this material, coincident with evidence of improvement as judged clinically, which persisted through the remainder of the period of treatment. His symptoms returned twenty-four hours after the cessation of therapy. This patient also developed a pronounced eosinopenia, as may be noted in Figure 2.

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In view of the possibility that the poor clinical response in these two patients may have been due to inadequate therapy with Concentrated Adrenal Cortex Extract, the third asthmatic was treated with a total of

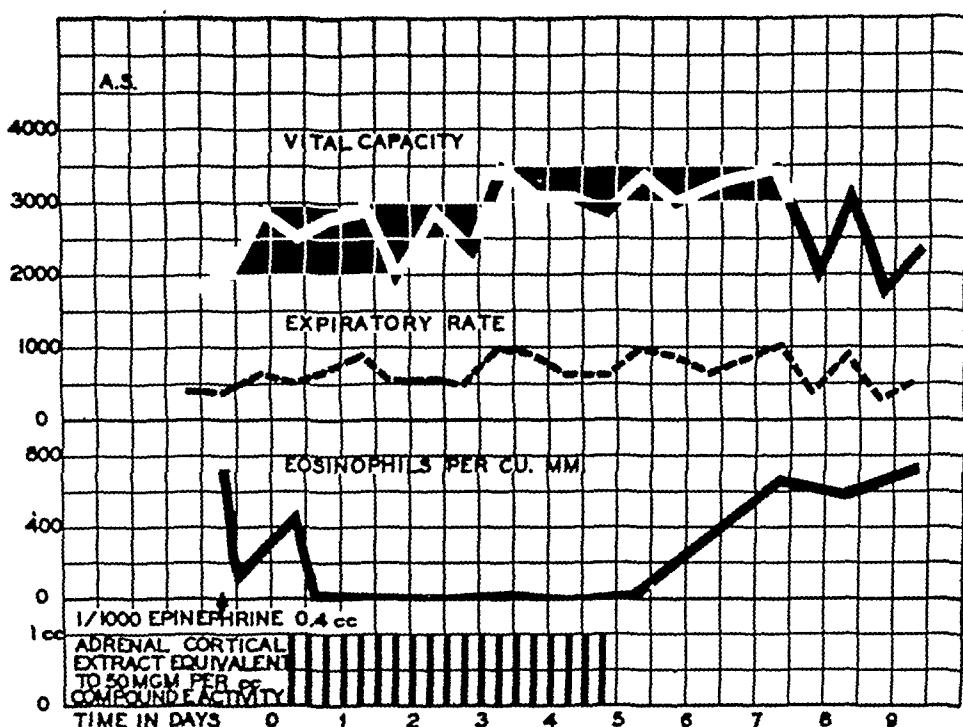


Fig. 3. Variations in the vital capacity, expiratory rate and peripheral blood eosinophils in A. S., a patient with bronchial asthma, following prolonged treatment with Concentrated Adrenal Cortex Extract.

19.0 c.c. of this material administered in doses of 1.0 c.c. every six hours over a period of five days.

Case 3.—This patient, A. S., a man, aged seventy-six years, had been subject to bronchial asthma since the age of sixty-two years. For a period of several months prior to his initial therapy with ACTH, he had been receiving oxygen, epinephrine and other symptomatic medications at approximate hourly intervals to control his asthma. He was hospitalized in August, 1949, and received a total of 325.0 mg. of ACTH in divided doses of 25.0 mg. every six hours. By the end of this period of treatment he was able to discontinue all symptomatic medications; his vital capacity had increased from 2,500 to 3,650 c.c., and his expiratory rate had changed from 400 c.c. to 2,500 c.c. of air per second. He was discharged from the hospital and required no symptomatic medications for the following twenty-one days.

In the following week he relapsed to his former level of symptoms, was rehospitalized and given a second course of 225.0 mg. of ACTH, and responded similarly.

Six weeks after the last course of ACTH and in a state of relapse, he was rehospitalized and treated with Concentrated Adrenal Cortex Extract intramuscularly in the above-mentioned dosage. Changes in his ventilation studies and level of peripheral blood eosinophils are shown in Figure 3. A gradual improvement in the severity of his asthma occurred while he was receiving adrenal cortex extract, but his chest was never completely free of rales and he continued to require symptomatic measures for the relief of wheezing. Asthma of the former degree of severity re-

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curred on the third day following the cessation of therapy, coincident with a return of his former level of blood eosinophilia.

This patient has subsequently responded to an additional course of 225.0 mg. of ACTH in a manner comparable to that of his initial two courses, as previously described.⁸

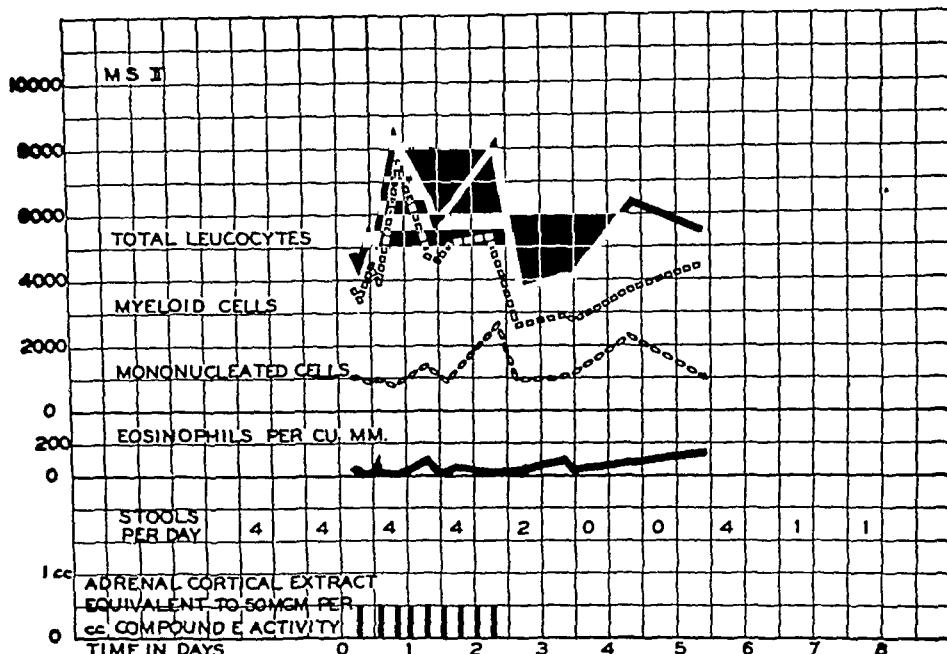


Fig. 4. Variations in the cellular elements of the peripheral blood as determined by glycol-stain counting chamber differential technique and the symptom response in M. S., a patient with gastrointestinal allergy, following treatment with Concentrated Adrenal Cortex Extract.

Case 4.—M. S., a woman, aged thirty-eight, had been under observation for three years with a diagnosis of gastrointestinal allergy. She was known to be highly sensitive to wheat in that its ingestion either accidentally or as a result of deliberate test feedings produced acute abdominal cramps and diarrhea requiring hospitalization. In August, 1949, this patient developed a recurrence of abdominal cramps and acute diarrhea having the characteristics of her previous attacks in spite of avoiding known allergenic foods. On the assumption that she had developed a spread of sensitivity to other articles of the diet, she was hospitalized and treated with 325.0 mg. ACTH in 25.0 mg. doses every six hours. On admission she was having between four and six liquid stools daily. Her diarrhea and other abdominal symptoms ceased after forty-eight hours of ACTH therapy. The day following this course of treatment she was returned to a general diet, including repeated doses of wheat, which she tolerated without a recurrence of her abdominal symptoms. She remained symptom-free on a general diet for a period of two weeks, then had a recurrence of diarrhea which was controlled for another week as a result of specific food avoidance. In spite of continued dietary measures she had a recurrence of abdominal cramps and diarrhea in the fourth week. She was then given nine doses of 0.5 c.c. each of Concentrated Adrenal Cortex Extract intramuscularly over a period of two days, as indicated in Figure 4.

Her abdominal cramps and diarrhea subsided by the end of the second day of therapy, and aside from a transient recurrence of diarrhea three days after cessation of treatment she remained symptom-free for the following two weeks even though

continuing to follow a general unrestricted diet. By the end of three weeks her gastrointestinal symptoms had recurred in their former severity and again were not controlled by the avoidance of wheat and the frequent use of aminophylline. In the past she had obtained a greater degree of relief of her severe abdominal pain as a result of the administration of aminophylline intravenously than from any other type of symptomatic therapy.

DISCUSSION

Although the intramuscular administration of Concentrated Adrenal Cortex Extract is effective in bringing about a marked diminution of the circulating eosinophils in a manner similar to that following the administration of pituitary adrenocorticotrophic hormone (ACTH), it is far less effective than ACTH in relieving the symptoms of chronic bronchial asthma. When given in large doses over a period of several days, Concentrated Adrenal Cortex Extract was slightly more effective than when administered for shorter periods, but in the one case in which this dosage schedule was tried it resulted in partial relief of asthma only during the period of administration. This agent seemed to be relatively more effective in bringing about relief of gastrointestinal allergic symptoms in the single case in which it was tried.

The relative failure of highly potent adrenal cortex extracts to relieve the symptoms of bronchial asthma when this condition may ordinarily be treated effectively by means of pituitary adrenocorticotrophic hormone (ACTH)⁸ and Cortisone⁹ is an interesting point for speculation. Selye¹³ has pointed out an apparent antagonism between the gluco-corticoids and the mineralo-corticoids. The injection of formalin in the hind paw of a rat in the presence of an excess of mineralo-corticoids (desoxycorticosterone acetate) produces experimental "formalin arthritis." The development of this reaction may be inhibited by treatment with ACTH or Cortisone. Selye¹⁴ further pointed out that some adrenal cortex extracts are rich in gluco-corticoids but they also contain mineralo-corticoids. In as much as adrenocorticotrophic hormone (ACTH) seems to stimulate the production of relatively more gluco-corticoids than mineralo-corticoids and Cortisone is a naturally occurring gluco-corticoid, the relief of allergic symptoms, including rheumatoid arthritis, with ACTH or Cortisone therapy may be the result of increasing the gluco-corticoid effect to counterbalance that of the mineralo-corticoids.

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THE RELATION OF ALLERGY TO CHARACTER PROBLEMS IN CHILDREN

A Survey

T. WOOD CLARKE, M.D., F.A.C.A., F.I.A.A.
Utica, New York

FIVE years ago a boy fifteen years of age was referred to me by the late Dr. Richard H. Hutchings, past president of the American Psychiatric Society and editor of the *Psychiatric Quarterly*. The boy had been sent to him with the expectation of placing him in a state hospital for mental diseases.

This boy, previously happy and amenable, had, for three years, suffered from attacks of acute excitement in which he would rage around the house smashing china and furniture. The attacks lasted about thirty minutes and usually were followed by sleep. He had had five such outbreaks in the five weeks before I saw him. The family had endured it to the limit of their endurance and had decided that he was a subject for a mental hospital.

Dr. Hutchings, in taking his history, found that he had had eczema as a child, and four years before had developed hay fever and asthma, which had lasted for two years. He had had no symptoms of allergic diseases for the last two years. However, as Dr. Hutchings was interested in the work I had done in his hospital on allergy in epileptics, and had published an article of mine on "Allergy of the Central Nervous System," he referred the boy to me.

Physical and neurological findings were not significant.

The first day's testing however showed 4+ reactions to oat and wheat. Later he reacted to feathers, fall pollens, cat dander, house dust and slightly to other foods. Oat and wheat were removed from his diet, and later desensitization inoculations were given for the inhalants.

The results of removing the oat and wheat from his diet were dramatic in the extreme. Almost overnight the boy's entire character changed. From being unhappy and apprehensive he became, in a very few days, happy and co-operative. He has had no outbreaks of temper for five years. He is friendly and full of fun. He is now doing well in college. This case—with that of a woman who had been admitted to the Marcy State Hospital some dozen times for episodic mental disorder and who at last said that she thought these were in some way associated with her asthma, who gave a strong reaction to dog hair and had a relapse of her psychiatric condition when a dog was brought into the ward—and that of a morose boy, who had been expelled from four schools as incorrigible, who cleared up emotionally when the foods to which he was allergic were eliminated, got good marks in school and became an enthusiastic Boy Scout—set me to wondering

Since the circulations of the two journals do not conflict, this article is also appearing in the current issue of *Psychiatric Quarterly* by mutual consent.

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Dr. Clarke is consulting allergist, Marcy State Hospital,

whether some of the mental changes which occur in what we designate as problem children might not be the direct result of an allergic cerebral edema such as we get in migraine and epilepsy of allergic origin, or of the chronic abnormal vasomotor activity of the cerebral vessels due to the constant allergic reaction resulting from eating some food or breathing some inhalant to which the "problem child" is allergic.

At the 1949 annual meeting of the American College of Allergists the matter was discussed with a number of the officers of the College. They were unanimously of the opinion that it was a subject worthy of systematic study. As I had been serving the College for five years as a member of the faculty of its instruction courses as lecturer on allergy of the central nervous system, it was agreed that I should investigate the subject for a year and report my findings at the next meeting of the College in January, 1950.

Very little attention has been paid to the relations of allergy to character in the medical literature. The first extensive articles on the subject were written in 1922 and 1924 by W. Ray Shannon¹² so long ago that allergy is referred to as anaphylaxis and the allergic diseases as sequels of the exudative diathesis. He described four children with allergic diseases and the "neurotic diathesis": one with allergic history, no present allergic symptoms, but great restlessness, and two with marked nervousness but no other manifestations or history of allergy, all of whom had positive skin reactions to foods. All seven of these lost all nervous symptoms as soon as the offending foods were removed from their diet.

Brief mention is made of psychological changes in allergic patients in articles by Hoobler,⁴ Kahn,⁶ Duke,³ Randolph,¹⁰ Rowe,¹¹ Clarke,¹ and Winkelmann and Moore,¹³ and more recently in the splendid article on cerebral allergy by Davison.² The textbooks usually give only a few lines to the subject.

In order to get a consensus of opinion of my allergist confreres on this subject, I sent a letter to all the allergists of the United States and Canada listed in "The Directory of Physicians Interested in Clinical Allergy" asking for their experiences with allergy causing deleterious character changes in children which cleared up when the allergic conditions were brought under control.

The response to these letters has been most gratifying. In all, 171 replies have been received. Of these, nine expressed the belief that allergy had nothing to do with personality, seven took the attitude that allergy was psychosomatic, that the allergy was the result of emotional conflict which made the patients problem children, fifty-eight said that either they took no children or had not had their attention called to psychic complications of allergy, and ninety-five assured me that they had noticed personality changes due to allergy which corrected themselves when the allergic element was eliminated. Many said that they had been thinking along the same line, assured me that they thought I was on the right track, and that

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calling attention to the relationship would be of value to both allergists and child psychiatrists. A few opinions are quoted:

"As you know, I have emphasized the psychological changes and effects on the nervous system in children due to chronic allergy for many years." (Albert H. Rowe, M.D.)⁹

"So often during the first visit no mention is made of the child's behavior, and the only concern with the parents is the presenting allergic symptoms. However, when the allergic situation has been brought under control, it is amazing how much emphasis is placed by the parents upon the altered behavior of the child. The stock phrase that is heard frequently is, 'He is a different child to live with.'" (Frank F. A. Rawling, M.D.)⁹

"I have seen a number of children in whom the correction or improvement of the allergy has been followed by definite lessening of the emotional instability and by better behavior." (Louis Tuft, M.D.)⁹

"There is no doubt in the mind of any physician who is practicing allergy that food sensitivities do bring about definite changes in children's behavior." (Abraham Colmes, M.D.)⁹

"On a number of occasions I have noted behavior problems occasionally of severe degree in children who are unquestionably allergic. I have found not infrequently that the behavior has improved to a marked degree when the allergy was controlled." (C. R. K. Johnston, M.D.)⁹

"It has been my observation for a long time that quite a large percentage of allergic children who come to me have considerable irritability and many of them are so-called problem children. Furthermore, the lessening of the irritability, and the greater ease with which these children are managed, closely parallels the improvement in the specific allergic condition for which they are being treated." (Gerald C. Grout, M.D.)⁹

"I certainly agree with your original premise regarding character changes in children suffering from allergic problems. One of the most pleasing and notable things in the treatment of children is this change for the better in their personal attitude and characteristics. One of my routine questions is asking mothers about this, and invariably the answer is that the child is physically better but tremendously improved in disposition, eating habits, sleeping, and general amiability." (Martyn A. Vickers, M.D.)⁹

"It is my impression and the impression spontaneously expressed by their parents that several small children who were excessively talkative, volatile and excitable have been quieter, more placid and much easier to care for after their allergies were brought under control." (Edna S. Pennington, M.D.)⁹

"A number of the children we see with asthma and perennial vasomotor rhinitis are often irritable, fussy, and difficult to manage. These symptoms improve as the allergy diseases mentioned are brought under control." (G. B. Logan, M.D.)⁹

"There have been numerous children who have been patients of mine that have been called problems by their parents, and after their allergies have been corrected the parents have remarked that there is all the difference in the world." (Katharine Baylis MacInnis, M.D.)⁹

"I am convinced that a considerable number of so-called problem children are allergic and that correction of this state of affairs will go a long way towards eliminating these undesirable characteristics." (John P. Henry, M.D.)⁹

"My experience has been that in quite a few children and during their allergic flareups, particularly asthma, there is a distinct psychic problem where the child is difficult to handle. As the condition is corrected or relieved, the patient's personality, his behavior, et cetera, change entirely for the better." (Sim Hulsey, M.D.)⁹

"Practically every day since I have been practicing allergy, mothers come in with

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the statement that 'Johnny is so irritable', or 'his disposition is so much better since he is on his diet', or that 'he is as mean as the devil when he eats a certain food.'" (Fannie Lou Leney, M.D.)⁹

"My most pertinent observation in this matter is that when a child is sent to us for allergy study who is in school, I find the grades, much of which you know is based upon adaptability, may be low. After a semester or a year of allergy control, these youngsters make a distinct rise in their class standing." (William A. Thornhill, M.D.)⁹

"Certainly anyone who has followed children's allergic troubles and their improvement under treatment has been impressed by this part of the problem. Certainly allergic management of the children makes a great difference for the better in their personalities and relations to other pupils." (John F. Pilcher, M.D.)⁹

"I have had mothers tell me that their children seem to be less irritable and better adjusted to school environment when their allergies are under control." (S. C. Mis-sal, M.D.)⁹

"We have had frequent cases of children with asthma in which we have had appreciative mothers say, 'I also am so happy that he (or she) is an entirely different child and is much more like other children. He is not so irritable; he is now a happy child.'" (Fred C. Endres, M.D.)⁹

Of these ninety-five allergists, forty sent me brief histories of 122 cases from their own experiences. Most of the others said that they had many times had cases in point, but as they did not have their files cross-indexed with this in mind they could not send me case reports.

In the 122 cases reported to me, the types of characteristics which were relieved by eliminating the allergy factor varied greatly. The most common reports were of irritable, fretful, quarrelsome children, who could not get along with others, often had to be taken out of school as they upset the classes and were considered incorrigible, who, after the nature of their allergy was discovered and proper steps taken to correct it, became friendly and happy and took active and joyous part in the occupations of their mates.

A few representative cases of the various types are reported briefly:

Case 1.—Age ten years. First seen with a history of cough, unexplained abdominal distress daily and irritability with some personality change over a period of four or five years. Intradermal skin studies showed positive reactions to several of the more common foods, principally corn, wheat, chocolate and orange. Gradual improvement followed avoidance of the offending allergens and at the time of the last visit on June 2, 1949, the patient was symptom-free. The patient's mother stated that it was difficult for her to believe, but she had finally been convinced that the complete reversal in the child's attitude and loss of irritability had accompanied improvement in the allergic symptoms. She further stated that prior to allergic management the child had never smiled and that now he is a very happy child. (Gerald C. Grout, M.D.)⁹

Case 2.—Age three years. A white male child had been seen by his pediatrician who felt that he had celiac disease because of his frequent large movements. His mother stated that his behavior was peculiar, that he would at times "act crazy." He cried almost constantly for the first eighteen months of his life. He was extremely irritable and highly excited. He had a lassiness that would come and go. On the basis of the history, we placed him on an elimination diet, eliminating milk, wheat and eggs and many of the other commonly incriminating allergenic foods.

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and he made sensational progress. We found him definitely sensitive to rice, milk and to a lesser extent wheat, and when these foods were included in his diet one could precipitate the old symptoms of excitement and bizarre behavior. He had been watched since 1946 and he has gradually improved. (Carl L. Mauser, M.D.)⁹

Case 3.—Age five years. Complaint: recurrent bronchitis, hay fever. Diagnosis: bronchial asthma. This five-year-old child was a typical allergically-ill child, thin, nervous, restless, irritable, unco-operative, unhappy. He had been withdrawn from nursery school during the past year because he was a "trouble-maker." The usual treatment was followed: removal of offending allergens, hyposensitization with house dust year round and prophylactic treatment with mixed ragweed pollen extracts. The results were quite spectacular in that this child has had no asthma since September, 1943. Rapid gain in weight, stamina and emotional stability occurred, and the child entered first grade in the fall of 1943 and has done very well. The boy is now a normal, happy, co-operative and pleasant child. (Arthur G. Baker, M.D.)⁹

Case 4.—A child two years old had atopic dermatitis, nervousness, irritability, and restlessness, and frequently awakened at night crying. This child is allergic to several foods. The eruption is improving, and the disposition parallels the eruption as far as improvement is concerned. When allergenic foods have been added to the diet, the skin eruption and the cerebral symptoms have been aggravated at the same time. (Milton Millman, M.D.)⁹

Case 5.—Age three and one-half years. Diagnosis: infantile eczema and mild perennial hay fever in July, 1946. A diagnosis of asthma was made in December, 1948. This child was extremely irritable, "spoiled," and the parents had an exceedingly difficult time in toilet training her. It was found that the eating of peanuts was the food which was responsible for her being extremely cross and irritable and difficult to control. Other foods were found to produce eczema and still others contributed toward asthma and hay fever. The omission of the offending foods resulted in a happy child, easily controlled. (George W. Owen, M.D.)⁹

Case 6.—An eleven-year-old white boy, an only child, had asthma for the past four years, worse at night. He had received numerous treatments, including penicillin, without any apparent benefit. Allergic skin studies were done. He was immunized against the inhalant factors, particularly house dust. Removal of the positive foods from his diet, namely celery, cauliflower, peas, citrus fruit, oatmeal and chocolate was carried out. He has shown remarkable improvement in his allergic condition, and his mother has also noted a considerable degree of improvement in his behavior. He was irritable, stubborn, rowdy and introverted. Since the institution of treatment and the elimination of the positive foods, the child has been free of his asthma, has shown a great degree of co-operation with his parents, his schoolwork has improved and in addition he has regained his friends. (James H. Putnam, M.D.)⁹

Other children were described as antagonistic, negativistic, and stubborn, youngsters whom nothing pleased, who refused to follow suggestions and went into rages when their slightest wish was ungratified, but who, when their allergies were corrected, became amenable, obedient and docile.

Case 7.—Age six and one-half years. Came in because of a perennial and seasonal hay fever. She was also emotionally upset, unco-operative and was considered to be a badly spoiled child. Tests revealed a sensitivity to ragweed pollen, grasses, and oak. Under perennial treatment the hay fever was well controlled, and she is now very co-operative and normal emotionally. (Samuel J. Taub, M.D.)⁹

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Case 8.—Age five years. White female child. First seen April 28, 1948, because of chronic cough, asthma, nasal allergy. She was placed on an anti-allergenic regime which included hyposensitization therapy. This youngster was frequently a marked problem at home. She would spit in the mother's face, kick her and would not obey either parent. She was contrary to all suggestions, and there was a great sleeping problem. She has improved remarkably both from an allergic standpoint and with regard to her disposition. Although she is not completely over her bad habits, there is definite improvement. (Carl L. Mauser, M.D.)⁹

Case 9.—Age six years, "nervous" all his life. Examination showed an eczema of the rectum. But the most outstanding item was a compulsive type of behavior problem, the child screaming, not from fear, but from anger, fighting, kicking, trying to destroy property, and all the time swearing and cursing vociferously, enunciated at the top of his voice in baby talk that was so indistinct I hoped the nurses did not understand what he was saying. The mother told me they had completely lost control of the boy. Punishment was of no avail. He was placed on an elimination diet. Immediately his instability quieted, his rectum healed, he was well behaved and cooperative on visits to the office. The addition of milk to his diet caused immediate reversal of his behavior problem, and the rectum began to hurt. With the removal of milk he again became quiet and well behaved. A second test gave the same results. (J. G. Little, M.D.)⁹

Others were boisterous, talking incessantly and over-loudly, constantly hyperkinetic, and inclined to be destructive, who, after adequate treatment, became gentle, respectful and quiet.

Case 10.—Age six and one-half years. Reported on April 6, 1949, with chief complaint of dry skin, stuffy nose and asthma on a few occasions. On intradermal testing he gave reactions to pollens (grass and ragweed) and many inhalants. He is being desensitized to the pollens, and to the inhalants with satisfactory results. The child is bright in school, hypersensitive, irritable, and strong-willed, and talks constantly, with a tendency to stutter. Since we started treatment the mother says that he stutters less, is greatly improved in his behavior, less irritable, and listens more attentively to his mother. (Saul W. Chester, M.D.)⁹

Case 11.—Child began during the first year of his life with nasal obstruction and drainage involving the nose and ears, continuing along throughout the winters. Later he had vomiting and coughing spells. At the age of four these were controlled with pollens and elimination of a few foods. He first reported at the age of six in 1945 during the early winter. Bacterials and house dust were used during the winters and pollens throughout the summers. Throughout the course of the three years that he was treated in the office he showed the widest imaginable personality changes. When he was under control, he came in and took his shots and left without any argument, but when he would slip, or when a new offender showed up, it would be almost impossible to retest or even give him his regular shots. This happened several times. "He varied from the most angelic to the most obstreperous child that I ever saw, depending on the degree of control that we had over the allergies." His school record and his association with other children went along with our experiences in the office. (W. H. Woern, M.D.)⁹

Case 12.—Age seventeen years. Asthma, allergic dermatitis; pale, undernourished, weight 85 pounds. She was generally disliked by her family, and two years previous to admittance had picked a saucepan from the stove and hurled the contents in her

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mother's face. She had eczema since infancy and many attacks of croup. She was three years retarded in her school work and was found to be sensitive to cat, dog, and horse hair and lactalbumin. Under treatment since August 1945, she has been free from her eczema and asthma without booster shots oftener than twenty-two to twenty-eight days. Her weight has increased 15 to 20 pounds, and personality changes have been such that she is no longer disliked at home. (C. A. Buck, M.D.)⁹

Case 13.—A boy of four and one-half years with bronchial asthma since seventeen months of age, allergic rhinitis (perennial and seasonal), probable gastro-intestinal allergy, history of infantile eczema. He was an extremely nervous, hyperactive, undernourished child with a high-pitched, strident voice, demanding attention. When allergic symptoms were controlled by diet, elimination of reacting inhalants in the home, and desensitization to molds and ragweed, the child became much quieter, more reasonable, less demanding, and his voice lost the strident quality and became calmer and lower in pitch. Although he still remained a very active youngster, he slept well except during periods when the molds were bad, his appetite improved, and he learned to eat many foods he would not taste before. In the first six months of allergic management he gained four pounds and in the second six months 7 pounds. (Louise O. Kappes, M.D.)⁹

A number of the children were described as bashful and timid, children who would cling to their mothers' skirts and weep if spoken to, who were marked introverts, depressed, always tired and without ambition. These children, after the allergy factor was removed, became extroverts, friendly and vigorous in their play.

Case 14.—Age eight years. Began his treatments September 1948, for an almost persistent sore throat and cold over the years. He was also a timid, very mild-mannered child who cried on the least provocation and objected to having anything done in the way of treatment. He was started with pollens and bacterials and carried throughout the winter with very nice relief until February of 1949 when he again began having these crying spells and got his feelings hurt at the most trifling things. House dust was added, and he immediately lost his symptoms until March 15 when they returned. Bermuda grass pollens were added and he again lost his complaints. At the present time he is a cheerful, well-behaved child who can get along with other children. (W. H. Woern, M.D.)⁹

Case 15.—An eight-year-old girl with typical, although fairly mild, recurring bronchial asthma and allergic rhinopathy. There was also rather chronic coughing between attacks. Allergic survey including environmental tests and elimination techniques proved the allergens to be house dust, animal danders, pollens and other inhalants. Foods were not shown to be significant. The patient was troubled by periods of obvious depression, unexplained spells of crying, and evidence of introversion. Appropriate allergic therapy completely eliminated asthmatic attacks and produced a marked improvement in the nasal symptoms and recurring cough. At the same time most, though not all, of the psychic disturbances disappeared. For example the child no longer cried or sat around unmoving for long periods of time. (Philip M. Gottlieb, M.D.)⁹

It has been interesting to see the number of cases reported in which children, who, owing to inattentiveness, have been problems to their teachers and have been obliged to repeat their grades, who, when their allergy

has come under control, have made startling improvement, not only in their scholastic standing but also in their school behavior. The listless have become active, the inattentive good students.

Case 16.—A boy, aged six years, whose allergy consisted of an allergic bronchitis with a questionable psychogenic factor, and a questionable perennial allergic rhinitis. His grades in school had not been satisfactory; he was irritable and showed other deviations from normal behavior. After his allergy was controlled on treatment, it was noted that his grades were definitely improved, he had a much better disposition and behavior, and it was felt that these changes in disposition were associated with control of his allergic problem. (C. R. K. Johnston, M.D.)⁹

Case 17.—A girl of nine years whose allergic symptoms included migraine, constipation, and frequent "colds." She lost thirty-five days of school from illness in 1947-1948. Despite an I.Q. of 140, her schoolwork was not entirely satisfactory. She made frequent mistakes in copying. She was "difficult" for her teachers, had a chip-on-shoulder attitude and imagined her classmates did not like her. Her pulse-accelerating food-allergens are tomato, cheese, pork, banana, mint and licorice. After all of these foods had been eliminated from her diet, her schoolwork has improved and her attitude toward teachers and classmates has become normal. She has lost only one school day in the past year from illness. Has a "cold" now only within two days after exposure to one of her food allergens. (Arthur F. Coca, M.D.)⁹

Case 18.—A six and one-half-year-old boy with spring and fall hay fever and a milder perennial allergic rhinopathy with cough. The patient was doing poorly in school, was antagonistic to his parents and often negativistic in emotional situations. Dust proofing of the bedroom and hyposensitization with pollens made, in the parents' own words, "a new boy of him." His schoolwork improved markedly so that he became one of the better pupils in the class, and the relationship with his parents showed improvement little short of amazing. (Philip M. Gottlieb, M.D.)⁹

Case 19.—A boy of nineteen years had nasal blocking and discharge for one year and frequent dull frontal headaches. He had been attending a Polytechnical High School for five months and was unable to concentrate. He was found allergic to milk, wheat, yeast, feathers, house dust and a few other foods. He felt much better, in two months on allergic diet and removal of feather pillows. Desensitization to wheat, yeast, and milk was undertaken because he found it so hard to eliminate these when living in a dormitory. In January, 1948, after one year of allergic regime, he reported that, whereas before the allergy tests were done he had flunked out in school twice, the last quarter he had made four A's. In another year he was graduated with honors and was accepted at one of the most difficult technological colleges to enter in the country. (Louise O. Kappes, M.D.)⁹

Case 20.—Age thirteen. This boy came to the office because of chronic sinus difficulty. In the course of taking the history the parents who were both present related the boy's mental sluggishness, retardation and inability to grasp his studies at school so that private tutors were necessary. He failed to make friends, was a good deal by himself and never enjoyed the usual games indulged in by boys of his age. Studies revealed the presence of pollen disease, particularly ragweed and also sensitivity to milk. The latter diagnosis was based chiefly upon a positive reaction to milk. The boy was put on pollen therapy, allergic cleanliness was instituted in his environment and milk in all forms was omitted from the diet. Within a week the mother reported that there had been a marked improvement in the nasal condition, and incidentally she remarked, "Somehow the boy is grasping his studies a little better and he seems

more companionable." Within another two weeks the tutor suggested that the boy return to school, and thereafter his studies were uninterrupted and school days were welcome to him. He commenced to encourage the friendship of other boys of his age, soon developed interest in baseball and started to lead a well-rounded life of studies and physical activities. The mother, unknown to the teachers of the school, introduced milk over a trial period and within two days the school reported that the boy was slipping again. He was again dull and his perceptivity was lessened, and he seemingly was headed for the same condition he was in before treatment was instituted. The omission of milk promptly relieved all the symptoms and thereafter the boy has made an uneventful recovery with the aid of pollen treatment. (Abraham Colmes, M.D.)⁹

Restlessness at night, crying out in sleep, nightmares, and enuresis have all been reported as disappearing with control of the allergy.

Various explanations have been given for these untoward characteristics in allergic children. Some are convinced that the constant, or recurrent, discomfort from the itching of eczema, or the respiratory difficulty in asthma so affect the child's stability that his mental equilibrium is broken down and his character changed. This is undoubtedly one cause of the condition, and the relief from the discomfort relieves the tension on his nervous system.

In many cases, also, over-solicitous parents, in order to compensate for their child's illness, and its consequent suffering, misguidedly remove all control over him and endeavor to see that his slightest and most unreasonable wish is promptly gratified. This attitude invariably ends in the little patient becoming arrogant, demanding, unhappy and furious when his desires are in any way thwarted. This is certainly an important element in the problem.

It has been interesting, on the other hand, to see how many of the reports received have stated that the writers have for long believed that in many of their patients there is a deeper, more intrinsic cause for the personality changes which their patients show, that there is some definite allergic reaction in the brain.

It is well established that a cerebral edema due to an allergic reaction in the brain tissue, or meninges, can be severe enough to cause migraine headaches,^{5,8} or convulsions⁷ usually classified as epilepsy. It is easy to imagine a situation where a reaction resembling giant hives in the cerebrum could cause emotional responses which would change the normal child into an uncontrolled brat. Sudden increase of intracranial pressure, which we know can occur from allergy, might well be the underlying cause of a temper tantrum, of over-excitement, or of any of the other psychic reactions with which we are so familiar in allergic children, and which are so dramatically described in the many letters I have received from the allergists of the United States and Canada.

In these letters I have received descriptions of children who, while they were allergic, showed none of the usual symptoms of the condition or were not suffering enough from them to account for their personality problems,

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still had such problems in severe form, and were relieved of them when the allergic factor was removed.

Case 21.—A girl of twelve years of age was referred because a cousin's disposition had improved markedly when an allergic condition had been cleared up. This girl showed no recognizable allergenic manifestations but had become such a problem that the mother said "she and her father can no longer live in the same house." An allergy study was made and the child was found to be sensitive to beets and asparagus. Asparagus was rarely eaten and could be disregarded. But it was found that she daily ate an ice cream cone made with beet sugar. When beets were stopped and the daily ice cream cone changed to one without beet sugar the change in this child "was of such a nature that one would have to be around the patient to appreciate the influence of the beet allergy on her personality." A ten-year follow-up on this case has shown her developing in a normal manner. (Herbert J. Rinkel, M.D.)⁹

Case 22.—A schoolgirl, aged ten, had become a severe behavior problem, and her mother was at her wits end to know what to do with her. The child was exceedingly unruly. She would lie in bed and refuse to get up. She whined continuously and complained of transient abdominal pains. She would not go to school for weeks at a time, and she became more and more irritable. Although she showed none of the usual manifestations of allergy, unless the abdominal pains were due to a gastrointestinal allergy, she was referred for a study. A complete physical and laboratory examination was entirely negative. Careful review of her dietary habits revealed that she was eating large quantities of chocolate. Allergic investigation showed marked sensitivity on cutaneous testing to chocolate and several other common foods. The offending foods were withdrawn from her diet with complete alleviation of her symptoms. The foods were returned again one at a time until she was given chocolate, at which time her symptoms returned. Chocolate and cocoa in all forms were immediately removed from her diet, and since then the child has been well and happy and makes no objection to going to school (E. L. Grinnell, M.D.)⁹

Case 23.—A five-year-old boy was referred by a pediatrician because of coughing, sneezing, post-nasal drip throughout the year, worse in the spring and fall. The child was nervous, irritable, easily upset, inclined to whine or cry at little things. Following allergic management which included allergic diet, removal of feathers, and dust precautions, desensitization to molds, ragweed, and grass, his disposition improved a great deal and his sneezing, sniffling, and coughing ceased. He became a happy, co-operative child. His father remarked, after the child had been under treatment for a year and a half, that he could tell when the boy needed a mold injection by a change in disposition before any nasal symptoms started. (Louise O. Kappes, M.D.)⁹

Case 24.—This boy, the son of an allergist, at the age of eight had frequent hives and at times slight nasal allergy and gastric-intestinal symptoms believed due to drinking milk. He was found to be allergic to milk and eggs. Later it was found that when this boy touched milk he manifested symptoms. He would immediately become very sleepy and would have to lie down and sleep. Upon awakening his eyeballs were very bloodshot and he felt very groggy. This was a great handicap to him in going through college because if he touched any milk he would not be able to study that evening, and it was necessary for him to remain out of college one semester in order to stabilize himself and get on to a special diet. On returning he did not return to his fraternity house but lived outside and boarded in a cafeteria where he could select his own food. The action of eggs on this boy was just the opposite. Instead of being lethargic it apparently made him nervous and he could not concentrate on his mental work but was more apt to go to the shop and begin

working with his hands and busying himself in that way. There was a definite difference in those two foods. At the present time, which is about fifteen years later, he has been able to eat eggs but still has to avoid milk in any form. (H. D. Parkhurst, M.D.)⁹

The lad I reported on at the beginning of this paper illustrates this situation. He had had no physical evidence of his allergy for several years and between attacks appeared quite normal except for his anxiety over his outbreaks. His family had not pampered him. Can one account for his temper outbursts better than by a sudden increase of intracranial pressure, or a cerebral vasomotor abnormality? The immediate disappearance of the outbreaks on removing the oat and wheat from his diet is certainly evidence that they were of an allergic nature.

Allergy is selective. In one person it can affect the skin and no other region. In another it will light upon the bronchial tubes alone. In others the nose, the eyes, the ears, or the gastrointestinal tract may be solely involved. We know that it can affect the motor areas of the brain and cause convulsions, or paralyses, or other areas and produce migraine. Is it too much to imagine that it can strike the psychic centers in the frontal lobes, and these centers alone, and cause character changes? Such character changes, due to an allergic reaction, can well result in the making of a "problem child."

The "problem child" rarely has a pleasant life. He is punished for being naughty and disobedient. He has a difficult time in school, is disliked by his teachers and hated and tormented by his schoolmates. If his characteristics are due simply to a mean and selfish nature, he may get his just deserts: if they are due to faulty home training, his parents certainly get theirs. If, on the other hand, they are the result of a mental illness, he deserves great sympathy and every possible effort to correct the underlying physical or mental cause. If the cause is an allergic reaction either in the brain or in any other part of the body, he deserves a thorough allergy study. A little time spent on this may change the whole course of a child's life. Allergy tests and appropriate treatment may be far more effective than either beatings or other forms of punishment.

The "problem child" frequently grows up to be a normal, although often an erratic, adult. He may, however, end up as a true psychotic. Today some of our state hospitals are erecting separate buildings for the care of "problem children" in the hope that by their early treatment the psychic seeds may be rooted out and future psychoses forestalled. If every child who has to be sent to a state hospital, or every "problem child" seen in our offices, or child guidance clinics, could be given a thorough allergy study, it is not too much to hope that some, perhaps many, would be found to be allergic, could have their allergy treated and could be returned to their homes normal emotionally as well as physically. The boy I reported at the opening of this paper appeared to be on the straight road to insanity. Dr. Hutchings' appreciation of the influence of allergy on the central

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nervous system may possibly have saved this lad from a violent ward of a state hospital.

If allergists would pay more attention to the psyche of their child patients, if child psychiatrists would appreciate that psychosomatic medicine can travel in reverse gear, that physical allergy of the brain can cause emotional changes, and if the two would co-operate in the study of the "problem child" from both the allergic and psychic angles, we may well hope that our state hospitals may not need such extensive facilities for the care of children, that many children may cease to be problems, and fewer adults become psychotic. The subject is deserving of systematic study.

Acknowledgment

The author wishes to express his sincere thanks to the many allergists who have made this survey and paper possible by their co-operation in expressing their thoughts on the question and reporting their cases.

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DISCUSSION

DR. HAL M. DAVISON, Atlanta, Georgia.—Just as in the case of most other physicians, for a time I considered mental and emotional symptoms occurring in allergic patients to be either a coincidence or secondary symptoms caused by the discomfort of the disease. The fact that following appropriate treatment these symptoms and the allergic symptoms disappeared together ruled out the first possibility. The fact that the mental and emotional symptoms occurred at times without other known allergic symptoms, and that they could be reproduced at will by feeding certain foods without producing other allergic symptoms, ruled out both the first and second possibilities.

Dr. Clarke's paper removes any possible doubt that these symptoms must be considered the direct result of allergic reactions in the central nervous system. Bray, a pediatrician of London, was one of the first to describe personality changes in chil-

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dren due to food sensitivity. Dr. Clarke has referred to other writers and has given you reports from many other physicians. These children, without the foods in their diet and with the foods in their diet, are literally Dr. Jekyll and Mr. Hyde. Their parents are equally pleased and astonished by the improvement in the patient following allergic management.

In the paper, "Cerebral Allergy," referred to by Dr. Clarke, we reported eighty-seven patients, five of whom were in the first decade of life and eleven in the second. The remaining seventy-one were scattered through practically all ages above twenty. The symptoms in adults and in the youngsters varied very little. We wish to stress the following:

Sleepiness on the one hand and insomnia on the other.

Sluggish thinking, inability to concentrate.

Childish compulsions.

Sense of unreality, as if patient were living in a dream.

Inability to be pleased about anything.

General unhappiness.

Morbid depression.

Loss of pride.

Loss of interest in the other sex.

I hope that Dr. Clarke will continue his observations along these lines, not only in children but in adults. I wish to stress again the fact that it now appears that practically any symptoms in humans may be caused by allergic reactions, and that when we have a symptom we cannot demonstrate any other cause for, we should think of allergy. Also, when we have symptoms occurring in patients who have other allergic manifestations, or a strong family history of allergy, we should always consider allergic reactions as a possible cause of their trouble.

In closing, I wish to quote the remark of one of my patients: "It is easy for me to follow your philosophy of life when I am on a diet, but impossible when I am not."

CONCENTRATED ADRENAL CORTEX EXTRACT

(Continued from Page 174)

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CERTAIN VASCULAR EFFECTS OF HISTAMINE AND d-TUBOCURARINE IN MULTIPLE SCLEROSIS

Part III

HINTON D. JONEZ, M.D., F.A.C.A.

Tacoma, Washington

THE theory that multiple sclerosis is a disease of allergy^{14,17,20,31,34,38,39,40} has been gaining acceptance to a great extent during the last few years. Dr. Tracy Putnam, Chairman of the Medical Advisory Board, National Multiple Sclerosis Society, stated before a United States Senate Committee on May 10, 1949, in part: ". . . At last we began to have some tangible facts about multiple sclerosis. Its allergic origin, at least in some cases, was confirmed."

In the Multiple Sclerosis Clinic at St. Joseph's Hospital,^{27,28} we have been treating this disease as one of allergy for the past three years.

Histamine diphosphate is given for hyposensitization^{15,37} and vasodilation.^{10,16,19,23,42} d-Tubocurarine chloride in oil and wax is used to aid in the control of spasticities, also as an adjunct in muscle re-education. Late-ly we have added vitamin B₁₂ to our therapy.

The methods of Horton^{5,24,25,26,33,34,36} are used for subcutaneous and intravenous¹¹ administration of histamine. For the past year patients on leaving the clinic for home have been placed on histamine iontophoresis by self-administration, using the technique as described by Abramson.^{2,3,4}

The question arose as to the length of time of the pharmacological action of histamine by the various methods of its administration. We know that histamine is a normal constituent of blood,³⁰ the concentration in human blood being from 1 to 8 micrograms per 100 c.c.⁸ However, artificially introduced histamine cannot be traced in the blood or urine since it is rapidly destroyed by a blood ferment, histase.¹ At our clinic we noted that venous blood when drawn while histamine was being injected was redder and more arterial-like in appearance. This observation suggested that a quantitative study of the oxygen content of the blood be made. In 1944 Peters, Horton and Boothby³⁴ had shown an increase in oxygen consump-tion during intravenous histamine injection (Van Slyke gasometric method). Also, in 1947 Grob, Lilienthal and Harvey²¹ reported measuring the histamine-like effects of an aqueous solution of curare by blood oxygen content (method not stated). The results of our studies are shown by Tables I to VIII.

TABLES

The oxygen content determinations of the venous blood in the following tables were performed by the volumetric method of Van Slyke and Stadie,

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**TABLE I. 2.75 MG. HISTAMINE DIPHOSPHATE IN 250 C.C. NORMAL SALINE,
INTRAVENOUSLY 45 DROPS PER MINUTE FOR 1½ HOURS**

Subject's Name	Before		During		Finish	1 hour later
	Volume	Per Cent	Volume	Per Cent	Volume	Per Cent
Wellman	10.8		15.3		16.8	11.2
Sister M.M.A.	10.3		15.7		16.3	10.1
Marquart	9.4		16.1		13.6	9.9
McTarnahan	9.4		15.5		9.9	8.2
Cleghorn	13.5		18.3		17.6	13.7

**TABLE II. 11.0 MG. HISTAMINE DIPHOSPHATE IN 1000 C.C. NORMAL SALINE,
INTRAVENOUSLY 45 DROPS PER MINUTE FOR 6 HOURS**

Subject's Name	Before		2 hours		4 hours		6 hours	2 hours later
	Volume	Per Cent	Volume	Per Cent	Volume	Per Cent	Finish	
Wick	12.6		17.5		17.8		18.0	8.1
Taylor	10.6		16.9		18.2		19.1	8.4

TABLE III. .275 MG. HISTAMINE DIPHOSPHATE SUBCUTANEOUS INJECTION

Subject's Name	Before		1 hour after		2 hours		3 hours	4 hours
	Volume	Per Cent	Volume	Per Cent	Volume	Per Cent	Volume	Per Cent
Marquart	10.2		11.6		11.5		11.0	10.2
Sister M.M.A.	10.5		11.8		11.5		9.0	9.9
Wellman	10.4		11.5		12.6		11.0	10.6

TABLE IV. BY IONTOPHORESIS 10 C.C. OF A 1% SOL. OF HISTAMINE DIPHOSPHATE AT 6 MILLIAMPERES FOR 15 MINUTES*

Subject's Name	Before		During		After 15 minutes		After 1 hour	After 3 hours	After 4 hours
	Volume	Per Cent	Volume	Per Cent	Volume	Per Cent	Volume	Per Cent	Volume
Rod	11.7		18.2		18.7		15.5	12.2	11.4
Sister M.M.A.	10.6		17.8		15.5		14.2	11.0	10.2
Gill	9.6		19.8		13.2		9.4	9.2	9.6
Sauer	10.8		20.8		19.3		15.6	10.4	8.4
Morrison	8.9		15.2		14.7		11.2	9.2	8.6
Flannery	10.2		13.9		13.9		13.4	10.5	8.4

using the Van Slyke volumetric apparatus. The oxygen content of venous blood varies normally from 10 to 18 volumes per cent, arterial blood normally 15 to 23 volumes per cent.

It can be observed by Tables I and II that the oxygen content of the venous blood reaches the arterial level during the intravenous injection of histamine. This arterial level is maintained throughout the time of administration, but drops back to the venous level within a short time after the injection is stopped.

As shown by Table III, the oxygen content is increased by subcutaneous injection. This increase lasts longer, but at no time does the oxygen content of the venous blood reach the arterial level.

By iontophoresis Table IV shows that the oxygen content of venous blood is increased to about the same level as by intravenous injection. However, the effects appear to be maintained longer.

*Histamine diphosphate suspension in oil and wax supplied through the courtesy of Endo Products, Inc.

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TABLE V. 30 MICROGRAMS B₁₂ (RUBRAMIN) BY SUBCUTANEOUS INJECTION***

Subject's Name	Before		After 1 hour		After 2 hours		After 3 hours	
	Volume	Per Cent	Volume	Per Cent	Volume	Per Cent	Volume	Per Cent
Larson	11.8		11.8		11.8		11.8	
Cleghorn	11.2		11.0		11.2		11.2	

TABLE VI. 30 MG. OF d-TUBOCURARINE IN OIL AND WAX DEEP INTRAMUSCULAR INJECTION***

Subject's Name	Before		After 1 hour		After 3 hours		After 6 hours		After 8 hours		After 24 hours	
	Volume	Per Cent	Volume	Per Cent	Volume	Per Cent	Volume	Per Cent	Volume	Per Cent	Volume	Per Cent
Flannery	10.4		15.8		15.8		16.1		16.7		18.1	
Cleghorn	13.5		13.5		13.9		15.3		16.1		20.9	
Rod	11.8		12.5		13.0		14.2		14.0		12.4	
Marquart	10.1		12.0		12.2		11.5		11.0		10.2	
Sauer	11.0		11.0		11.0		11.8		14.0		12.8	

TABLE VII. VERY SPASTIC QUADRIPLEGIA CASES
Large Daily Doses of d-Tubocurarine in Oil and Wax.
Blood Taken Twenty-four Hours after Last Dose

Subject's Name	Amount daily	Volume Per Cent
Hitchcock	15 mg.	11.5
Sauer	15 mg.	12.0
Cleghorn	22.5 mg.	15.6
Wood	22.5 mg.	14.2
Johnson	30.0 mg.	16.8
Sullivan	30.0 mg.	18.3

TABLE VIII. 1/2 C.C. OF A HISTAMINE DIPHOSPHATE OIL AND WAX SUSPENSION 2.75 MG. PER C.C. INJECTED DEEP INTRAMUSCULARLY***

Subject's	Before		After 6 hours		After 18 hours		After 24 hours		After 48 hours		After 72 hours		After 96 hours	
	Volume	Per Cent	Volume	Per Cent	Volume	Per Cent	Volume	Per Cent	Volume	Per Cent	Volume	Per Cent	Volume	Per Cent
Smith	11.4		16.2		16.2		16.4		16.4		12.9		11.6	
Knutson	10.2		14.8		13.6		12.7		12.4		11.2		10.6	
Sister M.M.A.	10.6		16.0		18.3		18.7		15.6		15.0		11.2	
Marquart	11.0		17.6		17.6		17.6		16.4		14.7		12.1	

Table V indicates that the subcutaneous injection of B₁₂ (Rubramin) does not increase the oxygen content of venous blood.

In Table VI it is easy to observe that d-Tubocurarine in oil and wax injected deep intramuscularly does increase the oxygen content of venous blood, and over a considerable period of time. This is probably because of the histamine-like effect of d-Tubocurarine. Table VII shows that the effect varies in different subjects but remains constant in relationship to the amount given. We believe the prolongation due to the repository menstruum in which the d-Tubocurarine was given.

The observation led us to use histamine diphosphate as a suspension, 2.75 mg. per c.c. in a menstruum of 2 per cent white beeswax and oxy-

*Powdered histamine diphosphate supplied through the courtesy of the Abbott Research Laboratories.

**Rubramin, Vitamin B₁₂ Concentrate, supplied through the courtesy of E. R. Squibb & Sons.

***d-Tubocurarine Chloride in oil and wax supplied through the courtesy of Abbott Research Laboratories.

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cholesterol derivatives dissolved in peanut oil. Code and Varco^{12,13} in 1940, later Greenblatt, Feldman and Linder²⁰ in 1949 reported the use of histamine in a retarding menstruum.

Table VIII indicates that when the suspension is given deep intramuscularly this results in an increase of the venous blood oxygen content up to ninety-six hours. In most cases the increase is to an arterial level for over forty-eight hours.

COMMENT

Brickner and Franklin^{6,18} in 1947 stated that the basic notion in the therapy of multiple sclerosis "calls for continued vasodilatation of the vessels of the nervous system, as well as for the prevention of spasm. Both these measures should be enforced for twenty-four hours a day. A drug-free interval of even a few minutes would suffice for an attack." Repository histamine may fulfill these criteria of therapy.

The possibility of producing gastric ulcers by the use of repository histamine³² must be considered. Code, Varco, Walpole, Wangensteen and Hay^{12,13,22,41} did produce them in dogs and cats by using histamine in beeswax. However, the dose used to do this was many hundred times the size of any dose we use. On the other hand, they did not produce ulcers in monkeys even though these were given the same large doses that had been used on dogs and cats. Bernstein^{6,7} reports the successful treatment of peptic ulcer in man by the repeated injections of histamine. In our use of histamine by all methods we have never had a case in which the gastric acidity was not controlled by the taking of food or alkalizing powders.

We have also used repository histamine on patients with asthma, migraine, urticaria, and angioneurotic edema. These patients suffered no unfavorable reactions. In these cases the histamine effects were the same as those produced by the other methods of its administration, except that the "histamine lift" appeared to last longer when the suspension was used.

During our series, we have treated 254 patients with multiple sclerosis by intravenous histamine injections. Of these 106 are now administering histamine to themselves at home by iontophoresis and twenty-four are receiving the histamine suspension at the clinic. Practically all patients have received d-Tubocurarine in oil and wax intramuscularly and many of them B₁₂ (Rubramin) by subcutaneous injection.

SUMMARY AND CONCLUSIONS

The Van Slyke and Stadie methods of venous blood oxygen content increase determination apparently can be used as a gauge in measuring the pharmacological effects of histamine in reference to its mode of administration.

The allergy theory of multiple sclerosis etiology and therapy, does not conflict with or displace the therapy calling for the prevention of vaso-spasm and continued vasodilatation.

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The deep intramuscular injection of a retarding histamine suspension appears to measure up to the criterion of continued vasodilatation.

Injection of repository histamine in the proper dose two or three times a week appears at present to be the proper time interval.

We are of the opinion that a repository histamine suspension may be used successfully wherever hyposensitization or continued vasodilatation is indicated, our Van Slyke oxygen content tests leading us to believe that the prolonged histamine-like action of d-Tubocurarine in a repository menstruum, as given to our patients with multiple sclerosis, has increased the effectiveness of their histamine therapy.

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DEPARTMENTAL COURSE AND RESEARCH FELLOWSHIPS IN PEDIATRIC ALLERGY

The Pediatric Department of New York Medical College announces a course in pediatric allergy to be held on Wednesdays, 10:00 A.M. to 4:00 P.M., October to March. The course, consisting of lectures and seminars, demonstrations of laboratory and clinical procedures, and animal experimentation, will be given by Dr. Bret Ratner and Pediatric Staff.

Two full-time fellowships in pediatric allergy, one starting July 1, the other January 1, are offered by New York Medical College. The fellowships, running from one to two years, consist of intensive training in immunology, animal research, and allergy. Information is obtainable from the office of the Dean.

HYP-O-ALLERGIC PENICILLIN

S. WILLIAM SIMON, M.D., F.A.C.A.

Dayton, Ohio

THE problem of when to give and when to refrain from giving penicillin has been before the medical profession since the drug was introduced and the physician was cautioned as to sensitization and possible reactions. In seriously ill patients there is no problem as the recovery of the patient is tantamount and possible sensitization or reactions are not even considered. However, in some acutely ill patients, penicillin is withheld at times, while other less efficacious drugs are used, rather than to chance sensitization and possibly prevent the use of penicillin on some later occasion. In those with a history of past reactions from penicillin, the drug is either not given or, if so, with considerable trepidation even with so-called "desensitization." Most reactions are minor and in most instances can be ignored, but there is a small group of patients who react more severely, at times alarmingly, in whom discontinuance of the drug is essential.¹⁹ In the latter, dangerous situations such as exfoliative dermatitis may result if penicillin sensitivity is not recognized promptly.^{10,13,21}

The skin test, so ably described by Peck and his co-workers,²³ lacks reliability, as reactions have developed after negative immediate and delayed tests and none have followed the frequent positive tests.² In some patients, sensitivity seems to be transient, and subsequent courses of penicillin may be given without trouble; others develop an apparent permanent sensitivity.^{21,23,26}

When penicillin acts as an antigen, either complete in itself or as a hapten in combination with human or bacterial protein,³⁰ the reactions have been divided into the following groups by Feldman¹²:

1. Allergic dermatitis of the contact type.
2. Drug and serum-like reactions.
3. Erythematо-vesicular reactions.
4. Tuberculin type reactions.
5. Arthus-like reactions.

All of these types, on repeated observations, may show wide variation in the degree of hypersensitivity to penicillin.^{4,11} There is apparently no correlation between a past history of personal or familial allergies, previous skin disease, drug intolerance, previous penicillin therapy or reactions referable to it and the incidence of reaction.^{15,25} Penicillin sensitivity has been found to exist in the absence of trichophytin sensitivity and may not exist in the presence of trichophytin sensitivity.²²

Dr. Simon is Chief, Allergy Clinic, Brown General Hospital, Veterans Administration Center, Dayton, Ohio.

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"Decapryn" Succinate "Minergic" Solution was supplied through the courtesy of The Wm. S. Merrell Company, Cincinnati.

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The only reactions we have considered are the two most common ones. Urticaria usually appears five to fourteen days after stopping the drug. The erythematous-vesicular reactions which are id reactions, very much like dermatitis medicamentosa, involve primarily the groins, legs, hands and feet, occurring usually within twenty-four hours of starting the drug and subsiding in three to four days after its cessation.^{2,15} Circulating antibodies have been demonstrated in the urticarial type but not in the erythematous-vesicular. The urticaria is the result of a mechanism analogous to that observed in the classic urticaria of serum allergy. The acute edematous swelling characteristic of the wheal is due to increased capillary permeability which follows the release of a histamine-like substance at the subpapillary level of the skin. The actual shock cells are probably located within the walls of the smaller vessels and capillaries in the corium.² A period of anergy generally follows for a week after cessation of symptoms.³¹

Rostenberg and Welch have proven that sensitization to penicillin may be produced in most persons by repeated injections.^{24,25} The literature abounds with the per cent of skin reactions produced, varying from 1.2 to 20 per cent and averaging roughly 5 per cent to crystalline penicillin.^{1,15,16,18,23,25,29} We offer no particular explanation for the 1.2 per cent given by Lepper and his associates, feeling that they were either very lucky, which is improbable, or that the patients were not followed for a long enough period to determine whether or not reactions from penicillin developed.

In the newer types of penicillin preparations, efforts have been made to impede the absorption so that blood levels are prolonged and the necessity of frequent injections removed. Penicillin in oil and beeswax⁹ which frequently produced pain at the site of injection, and occasionally indurations and even sterile abscesses, has been supplanted in favor of procaine penicillin. While beeswax was an infrequent sensitizer, in adding procaine to the penicillin, we have added another potent antigen.⁶ Penicillin blood levels with the latter are generally higher over a longer period than with the former and the procaine portion of the practically insoluble salt also gives a local anesthetic action.¹⁸

Caronamide has also been used to delay excretion of the penicillin and thereby prolong blood levels, but the consensus at present seems to be that the benefits achieved by raising the blood levels must be balanced against the dangers of administering sufficient caronamide to obtain this effect.^{14,17}

The question of blood levels in relation to therapeutic response has caused a great deal of controversy. We know many ways of raising and prolonging the raised blood levels but we are not in agreement as to the efficacy of this maneuver. It has not been demonstrated that continuous blood levels of penicillin are necessary or desirable for the treatment of all infections and a considerable amount of experimental evidence has accumulated which casts doubt upon this. Primarily, measurement of the blood

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penicillin level does not reliably indicate the concentration of penicillin in infected tissue.^{3,5,27} It is not necessary to maintain the blood and tissue concentration of penicillin continuously at effective levels in order to attain cure. Paradoxically, greatly increased concentrations of penicillin appear to decrease the death rate of certain organisms rather than to increase it. Obviously, the clinical response of the patient is a more reliable index to adequate therapy than laboratory determinations.^{7,8}

Therefore, we decided to use aqueous crystalline penicillin in this series, as its actions were limited rather than extended, no possible toxic substances or other antigens had been added, and we could make comparable blood level studies easier. However, to diminish or control the reactions we added to this penicillin an antihistamine dissolved in the diluent. Antihistamines have been found to be of value in treating penicillin reactions by competing with histamine for attachment to the cell receptors in the skin²⁸ so they should be of infinitely more value in preventing these reactions in the same way. We had found Decapryl (dimethylaminoethoxy-methylbenzylpyridine) Succinate to be superior to other antihistamines in this treatment and therefore preferred to use it in prophylaxis. Many animal experiments had shown injected Decapryl to be completely absorbed and nontoxic.

Combinations of Decapryl Succinate with various pharmaceutical forms of penicillin were evaluated for their effect, or lack of effect on penicillin blood levels in rabbits. The dosage of penicillin administered to rabbits in these studies was 30,000 or 40,000 units per kilogram of body weight. This dosage is based on a report that the percentage of animals showing concentrations of penicillin in the serum in excess of 0.05 units per c.c. following such dosage will equal the per cent of patients showing concentrations of penicillin equal to, or greater than, 0.03 units per c.c. following the injections of 1 c.c. (300,000 or 400,000 units) of the same preparation. These studies¹⁸ showed that Decapryl has little or no effect on the blood levels induced by various pharmaceutical forms of penicillin.

Diluent for the crystalline potassium penicillin G used consisted of normal saline to which was added Decapryl Succinate 5 mg. per c.c. The penicillin was uniform in that each c.c. contained 100,000 units of penicillin and 5 mg. of Decapryl Succinate dissolved in normal saline. Dosage was in varying amounts from 50,000 to 300,000 units or from 0.5 to 3.0 c.c. One patient received 1,000,000 units every three hours in 3 c.c. of Decapryl diluent (15 mg. Decapryl Succinate), night and day for fifteen days, without ill effect.

To have adequate controls, the entire hospital was divided into medical and surgical wards. All patients on the medical wards given aqueous crystalline penicillin were automatically given Decapryl-Penicillin while all patients on the surgical wards given aqueous penicillin received the same crystalline potassium penicillin G dissolved in normal saline but with nothing else added. The present figures deal with five months' experience, and

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although more patients have been given penicillin and Decaprym-Penicillin than have been noted, only those reported patients are included.

Of 400 surgical patients on aqueous crystalline penicillin, twenty-six (6.5 per cent) developed skin reactions (Table I).

TABLE I

	No. of Patients	Penicillin Reactions	Per Cent of Reactions
Decaprym-Penicillin	292	7	2.4
Controls	400	26	6.5

Of 292 patients receiving Decaprym-Penicillin there were seven reactions (2.4 per cent). (The residents in the hospital who were charged with making the individual reports of the reactions to the regular penicillin and also to the Decaprym-Penicillin were definitely on the lookout for skin manifestations developing in patients on the combination. Probably no patient who developed even a semblance of a rash after receiving Decaprym-Penicillin was left unreported, where it is easily conceivable that many patients who were given the drug but developed no reactions were not reported. Therefore, it is believed that the actual percentage of reactions to Decaprym-Penicillin is much less than the 2.4 per cent noted.)

One patient was a sixty-two-year-old man with arteriosclerotic heart disease, aortic stenosis, ventricular fibrillation, pulmonary infarct and bronchopneumonia. He was receiving besides 150,000 units of Decaprym-Penicillin every six hours, Heparin, Dicumerol and Digitoxin. The generalized maculopapular confluent rash, which was most marked on the trunk, arose after two days of medication. It did not fade or change materially, although Decaprym-Penicillin was discontinued, in the remaining six days that he lived.

The second patient suffered from bilateral hydronephrosis, lobar pneumonia, uremia, and obstruction of the neck of the urinary bladder. Decaprym-Penicillin was given in doses of 100,000 units every eight hours for nine days and 200,000 units every eight hours for another two days. At this time he developed a generalized maculopapular rash which later coalesced. Decaprym-Penicillin was stopped, and the patient's eruption cleared rapidly on 25 mg. of Decaprym by mouth every four hours. Because it was felt that the excretion of penicillin was impeded by the kidney pathology and that in reality the penicillin blood levels were much higher than would be expected with the dose received, penicillin blood levels were run two days after penicillin was stopped. At this time the blood level was 15.5 micrograms per c.c. and the blood urea nitrogen was 185 mg. per cent.

The third patient received 50,000 units Decaphyn-Penicillin every four hours for two weeks in the treatment of chronic bronchiectasis. At the same time he was given aerosol penicillin. He developed generalized urticaria, migratory arthritis, and low grade fever, which cleared rapidly on

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stopping all penicillin and administering Decaprym Solution by injection intramuscularly.

The fourth patient had pneumothorax with infection and was given Decaprym-Penicillin for eleven days in a dosage of 300,000 units twice daily. Urticaria developed on the eleventh day but cleared in one day on stopping penicillin and administering an antihistamine by mouth. Two days later Decaprym-Penicillin was again started and given without reaction.

The fifth patient was treated for lobar pneumonia with 100,000 units of Decaprym-Penicillin every eight hours for fourteen days, at which time he developed a mild urticaria with little pruritus. One day's treatment with oral antihistamines completely cleared the eruption. No further penicillin was given as it was not indicated.

The sixth patient who had a carcinoma of the left suprarenal area, possibly involving the kidney, received 300,000 units of Decaprym-Penicillin twice daily for five days. Eight days after the last dose generalized urticaria developed which cleared in two days without treatment.

The seventh patient had a very advanced Parkinson's disease, and in addition to 300,000 units of Decaprym-Penicillin every eight hours for fifteen days he was also receiving Artane orally. He had had hives at frequent intervals previously but none during the last five years. Generalized urticaria developed two weeks after the course of Decaprym-Penicillin was started.

Three luetics, all with histories of previous reactions to penicillin, were given 9,000,000 units of Decaprym-Penicillin each. Two of these had had urticaria and the other erythema multiforme previously when given penicillin, of such severity as to necessitate interrupting treatment. Two were given 300,000 units of Decaprym-Penicillin twice daily and the other 600,000 units of Decaprym-Penicillin once daily. All took the entire course without reaction and with good therapeutic response.

Five patients developed an erythematous vesicular rash from regular crystalline penicillin. On stopping medication the rash cleared. When this same penicillin was again tried, rash reappeared. On changing to Decaprym-Penicillin, in the same dosage, the rash did not recur.

One patient received 200,000 units of Decaprym-Penicillin every six hours for four days. At the same time he was being given penicillin troches in the treatment of peptic ulcer. He developed a stomatitis, undoubtedly from the troches, but never any reaction from the injected Decaprym-Penicillin.

Another patient received crystalline penicillin in a dosage of 1,000,000 units every three hours for ten days, at which time he developed a punctate macular rash of the face and forehead. Because he was suffering from multiple liver abscesses it was deemed necessary to continue penicillin. Therefore, he was immediately switched to 1,000,000 units of penicillin dissolved in 3 c.c. of Decaprym diluent (15 mg. Decaprym) every three hours. This was continued for eighteen days. The rash cleared completely within

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three days although the penicillin blood level was 12.8 micrograms per c.c. Good therapeutic effect was observed.

A patient who developed urticaria on regular crystalline penicillin was shifted to the same dose (100,000 units every eight hours) of Decaprym-Penicillin, and the urticaria cleared completely during the week he remained on this medication.

It can be seen that all patients who reacted to regular crystalline penicillin were not put on Decaprym-Penicillin as in the others they had had sufficient medication when the reaction occurred. Of the patients given Decaprym-Penicillin, 60 per cent had been given penicillin previously and 40 per cent were taking it for the first time. This information was not noted on the controls. Decaprym-Penicillin was given from one to eighty-two days and the average for all patients was 12.7 days (Table II). Dosage was from 100,000 to 8,000,000 units daily, with the average daily dose being 600,000 units and the average total dose for all patients being about 6,000,000 units. No changes were observed in the blood and urine examinations done before and after using Decaprym-Penicillin.

TABLE II. DECAPRYM-PENICILLIN

Duration of treatment	—1 to 82 days (average, 12.7 days)
24-hour dosage	—100,000 to 8,000,000 units (average, 600,000 units)
Total dosage	—200,000 to 40,000,000 units (average, 6,000,000 units)

When we first started using Decaprym-Penicillin, blood penicillin levels were performed on ten patients who were then on regular crystalline penicillin. These were checked against the levels twenty-four and forty-eight hours after shifting to Decaprym-Penicillin in the same dosage. Four were lower, two were higher and four were about the same. All were above detectable levels and therapeutic results were unchanged.

We were quite surprised to note detectable blood levels of penicillin after twenty-four hours when patients were given but one dose of 300,000 units of Decaprym-Penicillin.

Lately, in selected cases, we have been using Decaprym-Penicillin in oil which is crystalline potassium penicillin G 300,000 units, Decaprym (oil soluble—not the salt, succinate) 15 mg., and aluminum monostearate 2 per cent in each c.c. of sesame oil. This preparation was put up in 10 c.c. rubber-capped vials. Our results with Decaprym-Penicillin in oil have also been good in those penicillin-sensitive cases where it has been tried and thus far there have been no reactions in about forty patients. Penicillin blood levels have been about the same as with the same dosage schedule with Decaprym-Penicillin at one, four and eight hours and somewhat higher at twenty-four hours.

However, the advantage of Decaprym-Penicillin in oil over Decaprym-Penicillin is not in slowness of absorption but that it is stable in solution at room temperature, is always available and is more easily washed from a syringe than the old oil and beeswax preparations. Decaprym acts as an

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excellent local anesthetic and either preparation may be injected into the deltoid muscle with no immediate or residual pain or tenderness. Patients shifted from regular aqueous crystalline penicillin to Decapryn-Penicillin have frequently remarked on the absence of pain and tenderness of the latter.

Work is in progress at present in treating many luetics with high dosage Decapryn-Penicillin in oil and this will be reported when completed. So far we have not attempted to use Decapryn-Penicillin intrathecally or in treating subacute bacterial endocarditis but this will be tried after suitable animal experiments.

DISCUSSION

For some years it has been known that antihistaminic drugs given orally at the time penicillin was being administered to patients with previous reactions would prevent some of these reactions from developing. We have gone one step further in preventing the development of penicillin reactions in many patients who, we believe, may have been sensitized to the drug.

Much argument might be forthcoming on the question of sustained high blood penicillin levels, but results lately seem at least as good with daily injections of sufficient aqueous crystalline penicillin. Procaine, another sensitizer, is not needed to delay absorption nor to act as a local anesthetic. However, it is possible that if the antihistaminic were added to procaine penicillin too it might prevent the development of reactions.

We have not attempted to measure therapeutic response with high level single dose crystalline penicillin versus Decapryn-Penicillin or Decapryn-Penicillin in oil, but the observations of others working with the Decapryn-Penicillin are that their results are at least as good as with the plain crystalline penicillin.

Side reactions to antihistamines given orally, which are extremely common, were not encountered in any of our patients. Penicillin and other drug reactions resulting in urticaria were treated by the use of intramuscular injections of 2 c.c. of the Decapryn diluent (10 mg. Decapryn Succinate) every three or four hours with better results than were obtained with any of the other common methods of treating this condition, including intravenous histamine.

It is a bit of arm chair philosophizing but the thought occurs that antihistaminics could be easily combined with other preparations which occasionally cause reactions and while possibly preventing these reactions, at the same time would make the injection of these remedies practically painless. To be considered are insulin, liver extract, vitamin B complex, thiamine chloride, et cetera.

SUMMARY

A new method of decreasing the number of penicillin reactions by the addition of an antihistamine (Decapryn) to the diluent is presented. In the

control group of 400 the percentage of reactions was 6.5, whereas in the group of 292 patients receiving Decapryl-Penicillin the percentage of reactions was only 2.4, which is a reduction in reactions of 63.1 per cent. The combination was practically painless on injection and the therapeutic results obtained were at least as good as with any other penicillin preparation now in use.

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(Continued on Page 289)

A WEEKLY MOLD SURVEY OF AIR AND DUST IN LEXINGTON, KENTUCKY

M. ELIZABETH WALLACE, R. H. WEAVER and M. SCHERAGO
Lexington, Kentucky

NEWTON, Scherago and Weaver (1948), in a study of the distribution of molds in outdoor air, indoor air, and house dusts in Kentucky, found differences in the mold flora of the different regions of the State which they studied. They also found differences in the mold content of the outdoor air, indoor air and house dusts. The extensiveness of their survey limited the number of samples that could be examined from any one locality. The present study was undertaken to study further the distribution of molds in outdoor air, indoor air and house dusts, using a single region (Lexington, Ky.) for the collection of a larger number of samples. Also; since both Sabouraud's agar and potato-glucose agar have been used recently in mold studies, the comparative values of the two media for the primary isolation of molds have been investigated.

MATERIALS AND METHODS

Modified Sabouraud's agar (Newton et al, 1948) and Bacto-potato-glucose agar were prepared with the pH adjusted to 3.0. One poured Petri plate of each medium was exposed for fifteen minutes to the outdoor air at the Kentucky Agricultural Experiment Station Farm and on Main Street, and to the indoor air at the Kentucky Theater, a residence in the southwestern section of the city, and a residence in the southeastern section of the city. Dust samples were also collected at the three indoor locations.

Exposures were made every seven days from July 20 through August 31. Then the residence in the southeastern section of the city had to be dropped from the survey list, and exposures at the remaining four locations were continued through September and October. A second brief survey was made at all of the original locations during the month of January. Exposures were made on January 4, 11, and 18.

After exposure the plates were incubated at room temperature until the colonies reached maturity. Then, the colonies of each of the macroscopically similar types of mold were counted and a representative of each type was subcultured on potato-glucose agar. The dusts were streaked out on plates of both Sabouraud's medium and potato-glucose agar, and subsequent procedures were the same as for the exposed plates.

Moist chamber cultures on potato-glucose agar adjusted to pH 5.6, were used for the microscopical identification of the molds.

A Manual of Soil Fungi (Gilman, 1945) was the chief reference used for the identification of the molds. Other references used were *The Asper-*

From the Department of Bacteriology, University of Kentucky.
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Dr. Scherago is an Associate Member of The American College of Allergists.

TABLE III. NUMBER OF COLONIES OF MOLDS FOUND
DURING THE SUMMER MONTHS

Mold	Potato Glucose Agar								Sabouraud's Agar									
	1*		3		4		5		1*		2		3		4		5	
	1*	2	A	B	A	B	A	B	1*	2	A	B	A	B	A	B		
Alternaria	50	115	0	158	0	81	0	0	35	98	0	135	0	49	0	0		
Aspergillus	245	257	62	392	62	475	11	81	180	201	31	213	15	107	13	58		
Monilia	0	0	0	0	0	0	55	0	1	0	0	0	0	0	0	0		
Mucor	0	0	0	0	36	0	19	0	0	0	0	0	19	0	39	0		
Oospora	13	8	0	0	18	0	0	0	10	1	11	0	16	0	10	0		
Penicillium	823	419	31	328	241	333	109	88	670	365	22	223	216	236	80	59		
Stemphylium	136	41	0	0	0	0	0	0	95	17	0	0	0	0	0	0		
Stachybotrys	3	61	0	0	3	0	0	0	2	22	0	0	4	0	0	0		
Undeveloped	0	0	1	0	3	0	0	0	0	1	0	0	1	0	0	0		

*1 = K. A. Exp. Sta. Farm, Outdoor Air.

2 = Main Street, Outdoor Air.

3 = K. A. Theater.

4 = Residence, SW section city.

5 = Residence, SE section city.

A = Indoor air.

B = House dust.

TABLE IV. PRODUCTIVITY OF SABOURAUD'S AGAR AND POTATO-GLUCOSE AGAR FOR GENERA OF MOLDS FOUND IN THE OUTDOOR AIR, INDOOR AIR AND HOUSE DUSTS DURING THE SUMMER MONTHS

Mold	Outdoor Air		Indoor Air		Dusts	
	Sabouraud's Agar	Potato-Glucose Agar	Sabouraud's Agar	Potato-Glucose Agar	Sabouraud's Agar	Potato-Glucose Agar
Alternaria	7.82%	7.21%	0.00%	0.00%	17.02%	15.49%
Aspergillus	22.40	22.03	18.03	17.01	31.97	35.26
Monilia	0.05	0.00	0.00	0.00	0.00	0.00
Mucor	0.00	0.00	11.36	13.13	0.00	0.00
Oospora	0.61	0.92	7.25	6.20	0.00	0.00
Penicillium	69.74	58.99	62.32	62.62	47.92	49.22
Stemphylium	6.58	7.77	0.00	0.00	0.00	0.00
Stachybotrys	1.41	2.91	0.78	0.43	0.00	0.00
Undeveloped	0.05	0.00	0.19	0.57	0.00	0.00
	99.69%	99.80%	99.93%	99.99%	99.91%	99.97%

gilli (Thom and Church, 1926), *A Manual of the Aspergilli* (Thom and Raper, 1945), and *The Penicillia* (Thom, 1930).

RESULTS

The results of the summer survey with potato-glucose agar are shown in Table I and with Sabouraud's medium in Table II. As can be seen from these two tables, the following molds were isolated and identified: *Alternaria geophila*, *Aspergillus fumigatus*, *Aspergillus luchuensis*, *Aspergillus niger*, *Aspergillus versicolor*, *Aspergillus* spp., *Monilia geophila*, *Mucor piriformis*, *Oospora variabilis*, *Penicillium albicans*, *Penicillium citrinum*, *Penicillium frequentans*, *Penicillium* spp., and *Stemphylium piriforme*. With both media *Penicillium citrinum*, *Aspergillus niger* and *Aspergillus fumigatus* were the most numerous and most widely distributed species.

The number of colonies of each genus of mold that were isolated from all five sources is shown in Table III. As can be seen from this table, the Station Farm consistently yielded the highest plate counts and the

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TABLE V. NUMBER AND DISTRIBUTION OF MOLD COLONIES UPON POTATO GLUCOSE AGAR DURING THE WINTER

NAME OF MOLD	KY. AGR. EXP. STA. FARM			MAIN STREET			MOVIE THEATER			RESIDENCE, SOUTHWESTERN SECTION CITY			RESIDENCE, SOUTHEASTERN SECTION CITY							
	Outdoor Air			Indoor Air			Dust			Indoor Air			Dust							
	Jan.	4	11	18	Jan.	4	11	18	Total	Jan.	4	11	18	Total	Jan.	4	11	18	Total	
Alternaria Geophilia Spp.	0	3	3	6	0	0	12	11	9	32	32	0	0	0	0	0	0	0	0	
Aspergillus Fumigatus Lichenensis Niger Versicolor Spp.	3	5	4	12	9	11	8	28	2	6	16	14	10	46	0	5	5	15	0	
Mucor Phormis	0	0	0	0	0	3	1	2	2	0	1	1	2	4	0	0	0	4	0	
Penicillium Citrinum Frequentans Spp.	15	18	14	47	7	10	5	22	3	3	8	17	16	17	53	4	3	5	12	
Stemphylium Piniforme	2	4	3	9	—	—	—	—	0	0	6	9	7	22	0	3	1	1	3	
Total	29	36	30	95	25	33	18	76	8	4	4	16	56	57	48	161	177	9	6	13
																28	27	23	84	
																112	32	36	23	
																91	23	14	22	
																59	59	159		

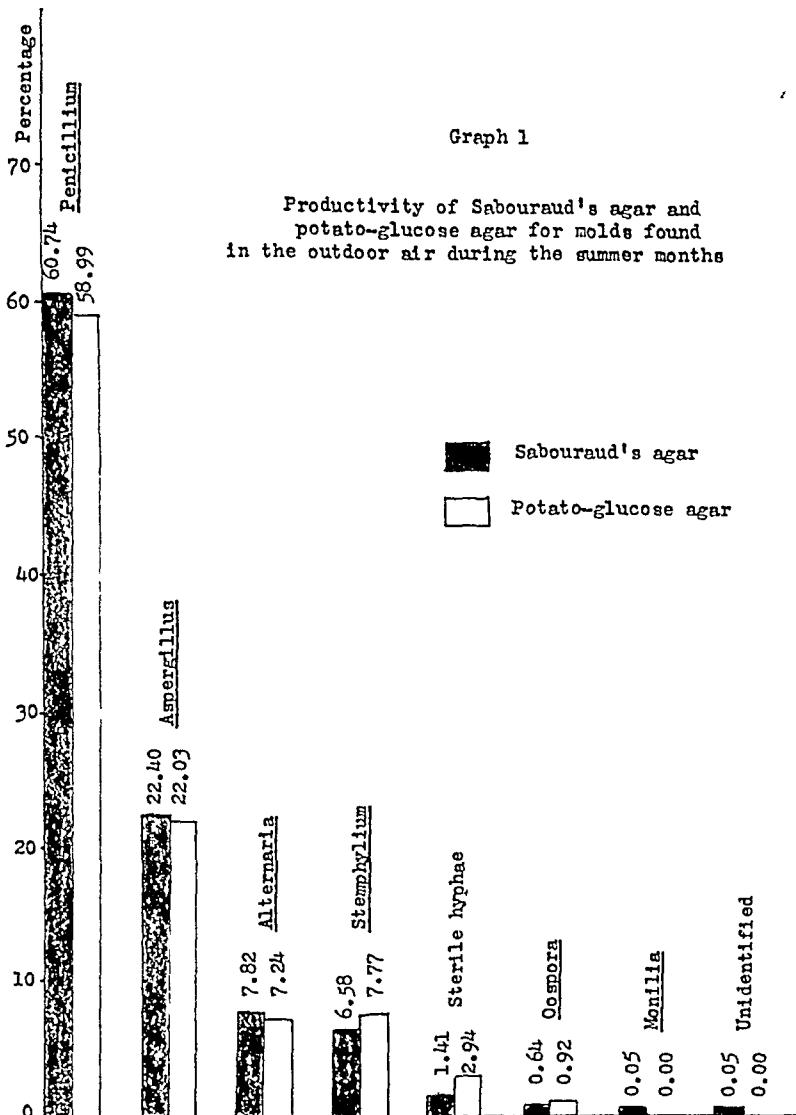
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TABLE VI. NUMBER AND DISTRIBUTION OF MOLD COLONIES UPON SABOURAUD'S AGAR DURING THE WINTER

NAME OF MOLD	MAIN STREET						MOVIE THEATER						RESIDENCE, SOUTHWESTERN SECTION CITY						RESIDENCE, SOUTHEASTERN SECTION CITY						
	KY. AGR. EXP. STA. FARM			OUTDOOR AIR			INDOOR AIR			DUST			INDOOR AIR			DUST			INDOOR AIR			DUST			
	Jan.	Jan.	Total	Jan.	Jan.	Total	Jan.	Jan.	Total	Jan.	Jan.	Total	Jan.	Jan.	Total	Jan.	Jan.	Total	Jan.	Jan.	Total	Jan.	Jan.	Total	
<i>Alternaria</i>	4	11	18	4	11	18	4	11	18	4	11	18	4	11	18	4	11	18	4	11	18	4	11	18	
<i>Geophilus</i>	0	1	1	0	0	0	0	10	8	6	21	21	0	1	2	2	0	0	0	0	0	0	0	0	
<i>Ashpergillus</i>	0	0	0	0	1	2	5	13	12	8	33	38	0	2	2	2	0	0	0	0	3	1	1	0	
<i>Fumigatus</i>	0	0	0	0	3	3	3	11	11	3	0	0	0	2	1	5	0	0	0	0	1	5	0	0	
<i>Luchuensis</i>	2	4	3	6	9	7	22	0	0	0	0	0	0	2	2	1	0	0	0	0	5	4	3	20	
<i>Niger</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	3	0	0	0	0	0	0	0	
<i>Versicolor</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
<i>Mucor</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
<i>Piniiformis</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
<i>Penicillium</i>	11	13	11	35	6	7	6	19	1	2	1	4	13	15	17	15	49	3	2	3	8	5	7	17	25
<i>Citriatum</i>	7	10	8	25	6	4	14	0	0	0	0	0	0	3	2	2	7	3	3	3	9	8	5	22	6
<i>Frequentans</i>	2	2	2	0	0	0	0	1	3	3	7	7	0	1	1	2	0	2	1	1	6	0	0	0	
<i>Spp.</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
<i>Stemphylium</i>	2	4	2	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
<i>Piniiforme</i>	2	4	2	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Total	22	31	26	79	19	20	17	56	2	4	3	9	40	43	37	120	9	7	7	23	12	13	15	40	
																								63	
																								19	
																								23	
																								10	
																								57	
																								16	
																								12	
																								40	
																								97	

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greatest diversity of species. This might have been due to the fact that the exposures were made near a barn in which cattle were housed; therefore, there was probably more dust in the air than at the other locations. The plate counts of the air in the Kentucky Theater were very low, but the

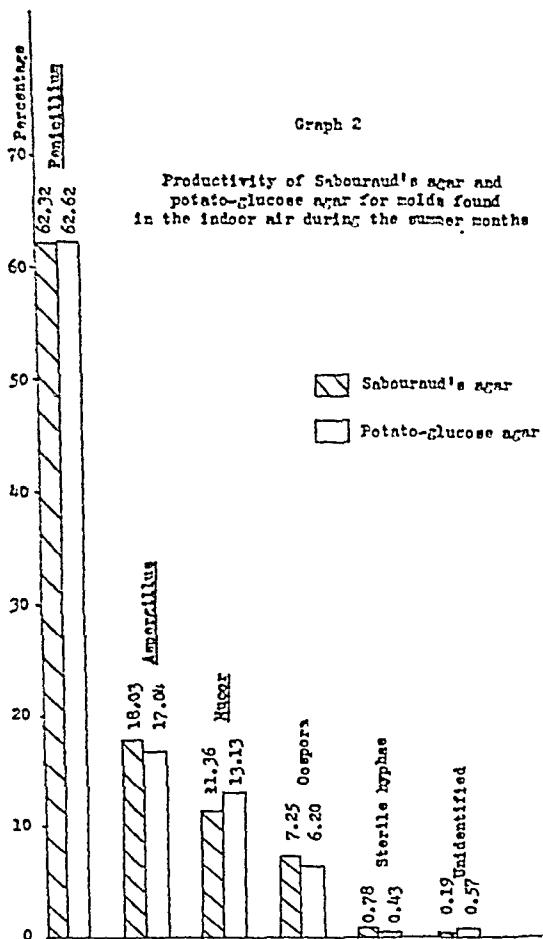


dust counts were relatively high. A possible explanation for the low "air" counts is the powerful air washing system that was in continuous operation at the theater.

Table III also shows that *Alternaria* was found in moderately large numbers in the outdoor air from both locations and in the dusts from the theater and the southwest residence although it was not found in the indoor air from the same locations nor in the dust or the indoor air from the southeast residence. *Aspergillus* was more prevalent in the dusts than in the indoor or the outdoor air. *Mucor* was present exclusively in the

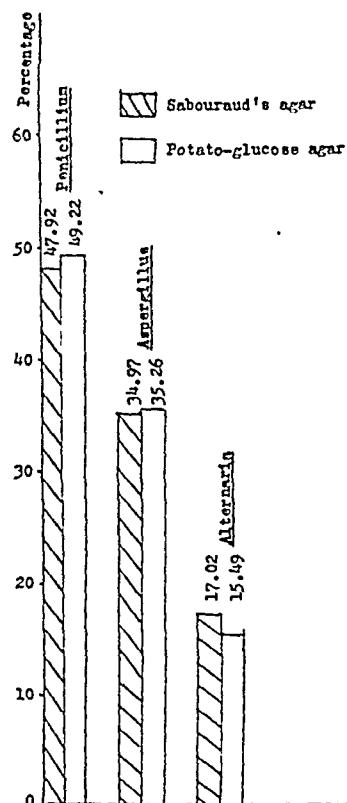
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indoor air. *Monilia* was found in significant numbers only in the indoor air from the southeast residence. *Oospora* was more abundant in the indoor than in the outdoor air and was not found in the dusts. *Penicillium* was present in high percentages in all three sources from all the locations.



Graph 3

Productivity of Sabouraud's agar and potato-glucose agar for molds found in house dusts during the summer months



Stemphylium was found exclusively in the outdoor air. A glance at Tables I and II will show that there was no appreciable variation in the species within the various genera of molds that were present in the indoor air, the outdoor air, and the dusts.

The difference in the productivities of the two media, as revealed in Tables III and IV and Graphs 1, 2, and 3, was apparently more quantitative than qualitative. There was generally a higher count of each mold on potato-glucose agar than on Sabouraud's agar, but there was no difference in the types that occurred, nor in the relative frequency of occurrence.

The results of the January survey are shown in Tables V, and VI; those with potato-glucose agar in Table V, and those with Sabouraud's agar in Table VI. From these two tables it can be seen that the following molds were isolated and identified: *Alternaria geophilolia*, *Alternaria* spp.,

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TABLE VII. NUMBER OF COLONIES OF MOLDS
FOUND DURING THE WINTER

Mold	Potato-Glucose Agar								Sabouraud's Agar							
	1*	2	3		4		5		1*	2	3		4		5	
			A	B	A	B	A	B			A	B	A	B	A	B
Alternaria	0	6	0	32	0	12	0	0	0	1	0	24	0	5	0	0
Aspergillus	12	28	8	57	4	24	25	30	9	22	5	44	5	9	17	17
Monilia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mucor	0	0	0	0	1	0	21	0	0	0	0	0	1	0	12	0
Oospora	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Penicillium	94	42	8	72	23	48	45	29	62	33	4	52	17	26	28	23
Stemphylium	9	0	0	0	0	0	0	0	8	0	0	0	0	0	0	0
Sterile hyphae	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Unidentified	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

*1—Ky. Agr. Exp. Sta. Farm, Outdoor Air.

5—Residence, SE section city.

2—Main Street, Outdoor Air.

3—Ky. Theater.

4—Residence, SW section city.

A—Indoor air.

B—House dust.

TABLE VIII. PRODUCTIVITY OF SABOURAUD'S AGAR AND POTATO-GLUCOSE AGAR FOR GENERA OF MOLDS FOUND IN THE OUTDOOR AIR, INDOOR AIR AND HOUSE DUSTS DURING THE WINTER

Mold	Outdoor Air		Indoor Air		Dusts	
	Sabouraud's Agar	Potato-Glucose Agar	Sabouraud's Agar	Potato-Glucose Agar	Sabouraud's Agar	Potato-Glucose Agar
Alternaria	0.75%	3.50%	0.00%	0.00%	14.50%	14.30%
Aspergillus	23.16	23.36	30.22	27.64	35.00	36.66
Monilia	0.00	0.00	0.00	0.00	0.00	0.00
Mucor	0.00	0.00	14.60	16.43	0.00	0.00
Oospora	0.00	0.00	0.00	0.00	0.00	0.00
Penicillium	70.97	67.74	55.03	56.77	50.50	48.43
Stemphylium	5.08	5.26	0.00	0.00	0.00	0.00
Sterile hyphae	0.00	0.00	0.00	0.00	0.00	0.00
Unidentified	0.00	0.00	0.00	0.00	0.00	0.00
	99.96%	99.86%	99.85%	99.84%	100.00%	99.39%

Aspergillus fumigatus, *Aspergillus luchuensis*, *Aspergillus niger*, *Aspergillus versicolor*, *Aspergillus* spp., *Mucor piriformis*, *Penicillium citrinum*, *Penicillium frequentans*, *Penicillium* spp., and *Stemphylium piriforme*. *Penicillium citrinum*, *Aspergillus niger*, and *Aspergillus fumigatus* were again the most numerous and most widely distributed species.

In Table VII are shown the numbers of each genus of mold isolated from each of the five sources during January on potato-glucose agar and Sabouraud's agar. In this table it can be seen that, as in the summer survey, the highest plate counts were obtained on the Experiment Station Farm. Again, the counts from the air in the Kentucky Theater were low and the dust counts were high.

The counts from the air during the January survey were lower than during the summer, but the dust counts were similar. No *Alternaria* were found in the outdoor air on the Station Farm and much less on Main Street than during the summer although it was equally prevalent in the dusts from the theater and the southwest residence. Also, no *Oospora*, *Monilia* nor *Penicillium albicans*, was found in the January survey. Other-

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TABLE IX. SUMMER/WINTER COLONY COUNTS OF MOLD GENERA FOUND ON POTATO-GLUCOSE AGAR AND SABOURAUD'S AGAR FROM OUTDOOR AIR, INDOOR AIR AND HOUSE DUSTS*

Mold	Potato-Glucose Agar			Sabouraud's Agar			Totals			Total
	Outdoor Air	Indoor Air	House Dusts	Outdoor Air	Indoor Air	House Dusts	Outdoor Air	Indoor Air	House Dusts	
Alternaria	165/6	0/0	242/44	133/1	0/0	184/29	298/7	0/0	426/73	724/80
Aspergillus	502/40	118/37	551/111	381/31	92/27	378/70	883/71	210/64	929/181	2022/316
Mouilia	0/0	0/0	0/0	1/0	0/0	0/0	1/0	0/0	0/0	1/0
Mucor	0/0	91/22	0/0	0/0	58/13	0/0	0/0	149/35	0/0	149/35
Oospora	21/0	43/0	0/0	11/0	37/0	0/0	32/0	80/0	0/0	112/0
Penicillium	1344/116	434/76	769/149	1035/95	318/49	518/101	2379/211	752/125	1287/250	4418/586
Stemphylium	177/9	0/0	0/0	112/8	0/0	0/0	289/17	0/0	0/0	289/17
Sterile hyphae	67/0	3/0	0/0	27/0	4/0	0/0	91/0	7/0	0/0	98/0
Unidentified	0/0	4/0	0/0	1/0	1/0	0/0	5/0	1/0	0/0	6/0
Totals	2276/171	693/135	1562/304	1698/135	510/89	1080/200	3974/306	1203/224	2642/504	7819/1034

*Colony count during summer given in upper part of rectangle, winter in lower part.

TABLE X. CLIMATIC CONDITIONS ON DATES OF EXPOSURES

Date	Mean Temperature	Wind, m.p.h.	Precipitation
July 20	64	2-5	none
27	76	15-20	none
Aug. 3	81	10-15	trace
10	79	8-10	none
17	80	8-12	none
24	80	6-8	trace
31	76	10-11	none
Sept. 7	77	6-9	none
14	72	6-14	none
21	73	30-35	none
Oct. 28	58	8-12	none
5	66	10-12	none
12	68	5-9	none
18	68	10-11	none
26	66	7-11	0.11
Jan. 4	32	20-25	trace
11	30	10-12	none
18	7	8-10	none

wise, there seemed to be no essential differences between the mold flora of the different locations during the summer and winter months. Again, as may be seen from Table VIII, there was little difference in the relative percentages of each mold on potato-glucose agar and Sabouraud's agar.

Table IX is a condensation of Tables I, II, V, and VI. From this table, it can be seen that: *Alternaria* was present in the outdoor air and in the dusts but not in the indoor air during both the summer and winter; *Mucor* was found exclusively in the indoor air in both surveys; *Oospora* was present in both the outdoor air and the indoor air but not in the dusts during the summer, and was not isolated at all during the winter; *Stemphylium* was found only in the outdoor air during both the summer and winter; *Aspergillus* and *Penicillium* were the most frequent and widely distributed genera in both the summer and winter surveys.

A record, Table X, was kept of the mean temperature, wind velocity and precipitation for each date of exposure. Other than the differences in results in the summer and winter surveys, already referred to, possibly due

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to differences in temperature, there seemed to be no significant effects produced by changes in weather.

Newton et al, in their survey, found that *Alternaria* was more prevalent in outdoor air than in indoor air and more prevalent in indoor air than in

TABLE XI. MOLDS FOUND IN ONE RESIDENCE BUT
NOT IN THE OTHER

	Southwest	Southeast
Indoor air	Aspergillus niger Penicillium frequentans —	— Aspergillus versicolor
Dust	Alternaria geophilus* Penicillium frequentans Aspergillus spp. Alternaria spp.** —	— — — Aspergillus versicolor

*Not found in the January survey.

**Found only in the January survey.

house dusts. This survey of Lexington only, indicates that *Alternaria* is present more often in dusts than in outdoor air and not at all in the indoor air. Newton et al also found *Hormodendrum* in large numbers in central and western Kentucky, while the present survey revealed none at all in Lexington.

These discrepancies may be explained by the fact that this survey was confined to one city while that of Newton et al covered a relatively large area in which Lexington was only one of many communities studied. Again, as is apparent from the present survey, there are distinct differences in the mold flora of various locations within Lexington, and it is possible that *Hormodendrum* and other types of molds would have been found if this survey had included the same exposure point as did that of Newton et al. Also, Newton et al made their surveys in January and in March, while the present surveys were made in the late summer, early autumn and January.

From the results obtained in this study, it would appear that potato-glucose agar would be more satisfactory than Sabouraud's agar for an accurate quantitative survey of an area. However, in order to determine the mere presence or absence of various mold species, it would make little difference which medium was employed.

Of interest is the observation that certain species of molds that were found in one residence were not found in the other. As shown in Table XI (compiled from tables I, II, V, and VI) *Aspergillus niger* and *Penicillium frequentans* were found in the indoor air in the southwest residence but not in the southeast, whereas *Aspergillus versicolor* was found in the indoor air in the southeast residence but not in the southwest. These differences in mold distributions were shown consistently on both media in both the summer and winter surveys. *Penicillium frequentans*, *Alternaria*

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geophilus, *Aspergillus* spp., and *Alternaria* spp. were found in the dust in the southwest but not in the southeast residence whereas *Aspergillus versicolor* was found in the dust in the southeast but not in the southwest residence. *Penicillium frequentans* and *Aspergillus versicolor* were found on both media and in both summer and winter. These findings emphasize the importance of making mold determinations at the house and the immediate surroundings of patients suspected of being sensitive to molds.

It is to be recommended that, within an area to be studied, various locations be sampled in order to determine more accurately and completely the mold flora. Since there is also a difference in the content of outdoor and indoor air and dust, these sources should all be included in the survey.

Since the major types of molds isolated during the summer and winter were virtually the same, a qualitative study need not be extended unduly. However, if a quantitative one is made, it should be conducted over a period of at least one year in order to determine the seasonal variations in numbers of molds isolated.

SUMMARY

A study has been made of the distribution of molds in indoor air, outdoor air, and house dusts from several sites in Lexington, Kentucky, on a large number of samples, using both Sabouraud's agar and potato-glucose agar. The results of this study have revealed the following:

1. *Penicillium* and *Aspergillus* were the most frequently encountered mold genera in both summer and winter from all sources of sampling.
2. *Mucor* was found exclusively in the indoor air.
3. *Monilia* and *Stemphylium* were found exclusively in the outdoor air.
4. *Alternaria* was present only in the outdoor air and in the house dusts. It was more prevalent in the summer than in the winter.
5. *Oospora* was present only in the air, not in the dust.
6. The air counts were lower during the winter than during the summer, although the dust counts showed no change.
7. There was no significant effect of any climatic condition except possibly temperature on the numbers or types of mold in the air.
8. Potato-glucose agar appeared to be more satisfactory for a quantitative study than Sabouraud's agar, although Sabouraud's is satisfactory for qualitative work.
9. Mold surveys for any region should include the examination of outdoor air, indoor air, and dust from several sites in that region.
10. The finding of different species of molds in two residences points to the importance of making mold determinations at the home and the immediate surroundings of patients suspected of being sensitive to molds.

(References on Page 228)

A STUDY OF THE ANTIGENICITY OF ATOPIC REAGIN

M. SCHERAGO and MARGO HASSON

Lexington, Kentucky

STUDIES on the antigenicity of antibodies have been made by a number of investigators. Claims of successful anti-antibody production have been made by Pfeiffer and Friedberger (1903) working with goat anticholera serum, Bordet (1904) working with rabbit anti-ox blood hemolysin, Yanagihashi (1928) working with rabbit amboceptor for sheep red cells, Keilhack (1935) working with rabbit precipitin, Barany (1935) working with horse and cow diphtheritic antiserum, and Foster, Scherago and Weaver (1940) working with rabbit *Salmonella pullorum* agglutinins. On the other hand the results obtained by Salfeld and Weichsel (1937) with diphtheria antitoxin, Humphries, Scherago and Weaver (1941) with syphilitic reagin, Treffers and Heidelberger (1941 a, b) with rabbit pneumococcus antiserum, and Kass, Scherago and Weaver (1942) with enzyme purified diphtheria antitoxin, cast some doubt on the antigenicity of antibodies.

Since no studies on the antigenicity of atopic reagin appear to have been made, it was thought worth while to make such a study.

EXPERIMENTAL

Experimental Approach.—Rabbits were injected with reagin containing sera from untreated hay fever patients that were known to be sensitive to short ragweed pollen. At the termination of the injections a portion of the antiserum obtained from each rabbit was absorbed with pooled normal human sera of blood groups A, O, and B, in order to remove any precipitins to normal human blood serum antigens. In addition, another portion of antiserum from each rabbit was absorbed with homologous reaginic serum to remove all the precipitins that had been produced.

To determine whether antibody to reagin had been produced, the portion of each rabbit antiserum that had been absorbed with normal human serum was mixed with varying dilutions of the homologous reaginic serum, and the mixtures were injected intradermally into normal* individuals. Twenty-four or forty-eight hours later, each skin site was tested with the homologous atopen to determine whether the rabbit antiserum had neutralized the reagin, as indicated by a negative skin reaction. In addition, the portion of each rabbit antiserum that had been absorbed with the homologous reaginic serum was injected into the same individuals, followed in twenty-four or forty-eight hours by the injection of atopen, to see if the reaginic serum had absorbed out any antibodies against reagin, as indicated by a

From the Department of Bacteriology, University of Kentucky.

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Dr. Scherago is an Associate Member of The American College of Allergists.

*Normal refers to persons who gave no history of allergy and who did not react to the atopen when it was injected into an unsensitized skin site.

negative skin reaction. Control injections were made with each reaginic serum, the absorbed rabbit sera, normal rabbit serum and the atopen.

Preparation of Materials.—

1. Reaginic sera. Reaginic sera from two untreated hay fever patients were employed in this investigation. One of the sera (X) was obtained from Dr. Kenneth P. Mathews of the University of Michigan, Ann Arbor, Michigan, the other (Y) from the Long Island College of Medicine, Brooklyn, New York. Serum X was from a twenty-two-year-old man who was sensitive to short ragweed; serum Y was from a twenty-four-year-old man who was also sensitive to short ragweed.

Approximately 50 ml. of serum had been collected aseptically from each of the patients, in sterile rubber stoppered bottles. Soon after each serum was received at the laboratory, it was sterilized by filtration through a sterile No. 02 Selas filter and dispensed into two sterile rubber stoppered vials which were placed in the refrigerator until further use. Immediately after filtration the filtrate was tested for sterility by streaking one drop of it on a blood agar slant and one on a nutrient agar slant. The tubes were incubated at 37° C. and observed for four days. No growth was produced by any of the filtrates.

2. Normal rabbit sera. The normal rabbit sera used in the investigation were obtained from animals that had not been previously used for experimental work. The serum from each rabbit was sterilized by filtration through a Swinny syringe type filter, tested for sterility as described for the preparation of the reaginic sera, placed in a sterile rubber stoppered vial, and stored in the refrigerator.

3. Normal human serum. Samples of normal human serum were obtained from nine persons, three each from blood groups A, B, and O, who gave no history of allergy. Twenty milliliter volumes of blood were obtained from one of the cubital veins and the sera were separated, using the same procedure as that used in separating the rabbit sera, pooled, and stored in a sterile rubber stoppered glass bottle in the refrigerator.

4. Allergenic extract. The short ragweed extract used in the investigation was obtained from Dr. Kenneth R. Andrews of Lexington, Kentucky. It was diluted with sterile physiological saline to yield a final dilution of 1:5000. This dilution was employed for all skin testing. The extract was stored in a sterile rubber stoppered vial in the refrigerator. Fresh dilutions were prepared as needed.

*Human Subjects for Prausnitz-Küstner Tests.—*Only persons who gave no history of allergy and who gave negative skin reactions to the test atopen were used for the Prausnitz-Küstner tests. Each reaginic serum was tested on two persons.

ANTIGENICITY OF ATOPIC REAGIN—SCHERAGO AND HASSON

Detail of Experiments.—

1. Preliminary procedures. (a) Passive transfer tests for the presence of reagin in the patients' sera.

In order to determine whether the two samples of sera from the allergic patients selected for this investigation contained reagin each serum was tested by the Prausnitz-Küstner method on two normal recipients. Both sera gave positive Prausnitz-Küstner reactions.

Each reaginic serum was retested every three weeks during the course of the investigation in order to see whether the reagin was diminishing in strength. At no time during the course of the investigation was there any evidence of a reduction in the strength of the two sera.

(b) Production and titration of rabbit antisera.

The immunization procedure that was employed in the preparation of the antisera against the reaginic sera was a modification of the method used by Dean and Webb (1926). Each of two young male rabbits was given two injections a week for four weeks with the reaginic serum against which it was to be immunized. The first two injections were given intravenously, and the six subsequent ones intramuscularly.

On the tenth day after the last injection, trial bleedings were obtained from the rabbits and the precipitin titers of their sera to the reaginic sera were determined by the micro-precipitin method.

The titer of the antiserum against reaginic serum X was found to be 1:1,600 and of the antiserum against reaginic serum Y, 1:3,200. Because these antibody titers were considered to be inadequate, a second series of two intramuscular injections a week for three weeks was given each animal after the animals had been given a rest period of five weeks. An outline of the schedule of injections is given in Table I.

TABLE I. SCHEDULE OF INJECTIONS
OF REAGINIC SERUM INTO RABBITS

Feb.	27	3 c.c.*
Mar.	2	3 c.c.*
	5	3 c.c.
	8	2 c.c.
	11	2 c.c.
	14	2 c.c.
	17	1 c.c.
	21	1 c.c.
	31	trial bleeding
April	26	2 c.c.
	29	2 c.c.
May	2	1 c.c.
	5	1 c.c.
	8	0.5 c.c.
	11	0.5 c.c.
	21	trial bleeding

*The first two injections were given intravenously; all the others were given intramuscularly.

Ten days after the last injection of the second series, a few milliliters of blood were drawn from the marginal ear veins of the surviving rabbits, and the precipitin titers of the sera were determined. This time the antiserum against reaginic serum X had a titer of 1:6,400, and the antiserum against reaginic serum Y had a titer of 1:12,800.

Although the precipitin titers were not as high as was desired the small amounts of the reaginic sera that were left had to be conserved for the rest of the experiment and could not, therefore, be spared for additional injections of the rabbits to increase the precipitin titers. The animals were, therefore, bled from the heart on the day of the trial bleeding. Approximately 70 ml. of blood were collected from each animal. The blood was allowed to stand at room temperature for one hour, after which it was rimmed with a glass rod and centrifuged at 1,200 r.p.m. for fifteen minutes. The serum was separated and placed in rubber-stoppered bottles and stored in the refrigerator.

(c) Absorption of the rabbit antisera.

Portions of the rabbit antisera were absorbed with normal human serum in order to remove antibodies to the proteins present in normal blood. For this purpose a mixture of normal sera from blood groups A, O, and B were used. For the absorptions, the procedure of Cumley and Irwin (1943) was followed.

Absorptions were also carried out on portions of the rabbit antisera with homologous reaginic serum. The purpose of these absorptions was to remove all the antibodies in the rabbit antisera, including the anti-reagin antibody if it was present. These absorptions were to serve as controls on the previous absorptions, since there was the possibility that anti-reagin antibody would be carried down with the normal serum antibodies (co-precipitated) in the absorption process. If the skin reactions with the rabbit antisera absorbed with normal human serum proved to be positive, the question would arise whether anti-reagin antibody had been present in the rabbit antisera. The removal of all the antibodies to the reaginic sera would help to clarify this point. If no antibody to reagin was induced, then the antisera absorbed with reaginic sera would contain free reagin and corroborate the results obtained with the antisera absorbed with normal human serum.

After each rabbit antiserum had been absorbed it was concentrated to its original volume by placing it in a sterile sausage casing, and evaporating it with the aid of an electric fan.

The concentrated antisera were sterilized by filtration through Selas 02 filters, dispensed in rubber stoppered bottles, and placed in the refrigerator until further use.

For the sake of convenience, the portions of the rabbit antisera that were absorbed with normal human serum were designated ARAN, followed by the letter of the reaginic serum with which the rabbits had been immunized, i.e., ARAN-X and ARAN-Y. Similarly, the portions of the rabbit antisera that were absorbed with their homologous reaginic sera were designated ARAH-X and ARAH-Y.

2. Prausnitz-Küstner tests to determine the presence of antibody to reagin in ARAN.

In order to determine whether the rabbit antisera, that had been ab-

sorbed with the pooled normal human sera; possessed anti-reagin that would neutralize reagin, four series of intradermal injections were made into normal recipients for each of the two samples of rabbit antisera. One hour before the initial injections were to be made, the materials for each of the four series of injections were prepared as follows:

Series A. Reaginic serum undiluted and diluted 1:5, 1:10, 1:20, and 1:80 with physiological saline.

Series B. Mixtures of equal volumes of ARAN and of homologous reaginic serum undiluted, and diluted 1:5, 1:10, 1:20, and 1:80, making the final dilutions of homologous reaginic serum 1:2, 1:10, 1:20, 1:40, and 1:160.

Series C. Mixtures of equal volumes of pooled normal rabbit serum and of reaginic serum undiluted, and diluted 1:5, 1:10, 1:20, and 1:80, making the final dilutions of reaginic serum the same as in Series B.

Series D. Two portions of 0.1 ml. each of previously prepared ARAH. The mixtures were shaken at various times during the hour to insure adequate distribution of the components in them. The normal rabbit serum used in this experiment was a pool of the sera from two animals.

The purpose of Series B was to determine whether the reagin had been neutralized by an anti-reagin antibody in ARAN. Into one control site (6) in this series ARAN diluted 1:2 with reaginic serum was used for the initial injection and physiological saline was substituted for the atopen in the second injection, to rule out any non-specific reactions. Into a second control site (7) in this series ARAN alone was used for the initial injection, to rule out any non-specific reaction between it and atopen.

Series A, C, and D were all control series. Series A was a quantitative Prausnitz-Küstner test and the reactions obtained in this series were to serve as a basis of comparison for those obtained in Series B. Into one control site (6) in Series A undiluted reaginic serum was used for the initial injection and physiological saline was substituted for the atopen, to rule out any non-specific reactions. Into a second control site (7) atopen alone was injected to make sure that the recipient was not skin sensitive to the atopen.

The purpose of Series C was to make sure that the normal rabbit serum itself did not neutralize the sensitizing ability of the reagin, at least not to the same extent as the anti-reaginic serum, so that any inhibition of the sensitizing ability of reagin in Series B could be unequivocally attributed to an antibody to reagin. Into one control site (6) in this series normal rabbit serum diluted 1:2 with reaginic serum was used in the initial injection and physiological saline was substituted for the atopen in the second injection, to rule out any non-specific reactions. Into another control site (7) normal rabbit serum alone was used for the initial injection to see if the rabbit serum itself would react with atopen.

The purpose of Series D was to make certain that the suspected antibody to reagin was not precipitated along with the normal human serum antibodies in the absorption procedure. If positive reactions were observed in

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TABLE II. SAMPLE PROTOCOL OF THE FOUR SERIES
OF INJECTIONS

Site No.	Initial Injections				Second Injection
	Series A	Series B	Series D	Series D	
	0.1 ml. reaginic serum	0.1 ml. of mixture of equal volumes of ARAN and reaginic serum diluted.	0.1 ml. of mixture of equal volumes of normal rabbit serum and reaginic serum diluted.		
1	undil.	undil. [†]	undil. [†]	—	0.02
2	1-5	1-5	1-5	—	0.02
3	1-10	1-10	1-10	—	0.02
4	1-20	1-20	1-20	—	0.02
5	1-80	1-80	1-80	0.1**	0.02
6*	undil.	undil.	undil.	0.1**	0.02***
7*	—	0.1 ml. ARAN alone	0.1 ml. normal rabbit serum	—	0.02

*Controls within the individual series.

**These injections were made at sites corresponding to sites 1 and 2 of the other three series, and are therefore designated as sites 1 and 2 in the text.

***0.02 ml. of physiological saline was substituted for the atopen.

[†]The final dilutions of reaginic serum were twice those listed.

both Series B and D comparable to Series A, it would be established that no antibody to reagin had been induced. On the other hand, if the reaction in Series B were positive while Series D was negative it would be an indication that co-precipitation had occurred in the preparation of ARAN. Into one site (2) of Series D ARAH was used in the initial injection and physiological saline was substituted for the atopen, to rule out any non-specific reactions.

The injections were made on the backs of the recipients to facilitate comparison of the reactions. The materials for the four series of injections were introduced into sites on the skin in four parallel vertical columns down the back and labelled with black ink. All tests were done in duplicate.

Immediately after the initial injections of the mixtures of reaginic serum and ARAN, and of reaginic serum and normal rabbit serum, and of ARAH, wheals and erythemas appeared at the sites of the injections in all the recipients. These reactions changed gradually, until purplish red areas of from 25 to 30 mm. in diameter remained after one hour. The color faded entirely in two recipients (E. E. and N. S.) within twenty-four hours, while in the other two recipients (C. C. and D. H.) the purplish red areas gradually shrank in size so that at forty-eight hours they were from 7 to 11 mm. in diameter. On the other hand, at the sites that were injected with reaginic serum alone there was only a slight reddening of the skin immediately after the injections, which disappeared within five to ten minutes.

Twenty-four hours after the initial injections the sites in recipients E. E. and N. S. that were to receive the atopen were injected with it, and forty-eight hours after the initial injections the corresponding sites in recipients C. C. and D. H. were injected with atopen. The atopen used had, on a previous occasion, elicited a Prausnitz-Küstner reaction in sites that had been sensitized with the reaginic sera employed in this experiment. Site

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TABLE III. MEASUREMENTS OF THE CUTANEOUS REACTIONS OBTAINED

Injection series	Site No	Tests with Serum X				Tests with Serum Y			
		Recipient C.C.		Recipient D.H.		Recipient E.E.		Recipient N.S.***	
		15 min	30 min	15 min	30 min	15 min	30 min	15 min	30 min
A	1	8x9 24x38*	7x7 24x32	12x11 55x44**	15x12 50x38	12x14 35x38	15x15 20x17	4x5 7x7	5x5 5x5
	2	7x9 22x24	6x7 22x26	10x11 50x75**	13x10 44x32	10x12 28x22	12x10 20x10	4x5 12x8	5x5 20x10
	3	5x10 20x22	7x8 21x16	7x7 43x29	8x11 40x29	5x8 14x10	5x5 10x10	5x6 20x26	5x4 20x25
	4	4x8 12x20	5x6 17x20	6x7 40x31	8x7 36x28	6x9 10x22	5x7 14x9	6x5 27x16	6x5 30x20
	5	5x6 10x10	5x7 11x9	5x7 40x28	8x6 39x28	3x6 3x6	5x5 5x9	2x4 2x4	neg
	6	neg neg	neg neg	neg neg	neg neg	neg neg	neg neg	neg. neg.	neg neg.
	7	neg neg	neg neg	neg neg	neg neg	neg neg	neg neg	neg. neg.	neg neg.
B	1	neg	7x7	10x8	neg	neg	neg.	neg.	neg.
	2	neg	20x16	45x35	neg	neg	neg.	neg.	neg
	3	neg	neg	neg	neg.	neg	neg.	neg.	neg
	4	neg	neg	neg	neg.	neg	neg	neg	neg
	5	neg	neg	neg	neg.	neg	neg	neg	neg
	6	neg	neg.	neg.	neg.	neg	neg.	neg	neg
	7	neg	neg.	neg.	neg	neg.	neg.	neg	neg
C	1	6x8 12x14	7x8 30x22	7x6 45x30	10x10 45x32	6x6 14x11	5x6 10x7	5x3 22x14	5x4 20x10
	2	6x6 6x6	8x7 10x11	5x4 35x30	neg	neg	neg	6x7 6x7	neg
	3	neg neg	neg neg	neg neg	neg neg.	neg. neg.	neg. neg.	neg. neg.	neg neg
	4	neg neg	neg neg	neg neg	neg neg	neg. neg.	neg. neg.	neg. neg.	neg neg
	5	neg neg	neg neg	neg neg	neg neg	neg. neg.	neg. neg.	neg. neg.	neg neg
	6	neg neg	neg neg	neg neg	neg neg	neg. neg.	neg. neg.	neg. neg.	neg neg
	7	neg neg.	neg neg	neg neg	neg neg	neg. neg.	neg. neg.	neg. neg.	neg neg
D	1	neg	7x7 15x15	5x5 30x20	4x5 30x24	neg	neg.	neg.	neg.
	2	neg	neg	neg	neg	neg	neg.	neg.	neg

*Wheal in mm x mm / erythema in mm x mm.

**The erythema of sites 1 and 2, Series A overlapped and were hard to measure.

***Site 1, 2 and 3 in Series A were difficult to locate for the second injection (atopen), since the recipient had washed off the ink label. Thus, some sites were probably missed when atopen was injected.

6 in each series received physiological saline as did one unsensitized site (site 7) in Series A. A sample protocol of the injections given each recipient is shown in Table II.

The reactions were observed fifteen and thirty minutes after the administration of the atopen (or saline). At each reading Kodachrome photographs were taken. The wheals and erythemas were measured and the two greatest diameters of each were recorded. The measurements are given in Table III. The skin reaction values were obtained by adding the four measurements. The results of the skin reactions are recorded in

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TABLE IV. REACTION VALUES OF CUTANEOUS REACTIONS

Injection Series	Site No.	Values with Serum X in Recipient				Values with Serum Y in Recipient			
		C.C.		D.H.		E.E.		N.S.	
		15'	30'	15'	30'	15'	30'	15'	30'
A 0.1 ml. reaginic serum.	1*	79	70	122	115	99	67	23	20
	2	62	61	146	99	72	52	29	40
	3	57	52	86	88	37	30	57	54
	4	44	48	84	79	47	35	54	61
	5	31	32	80	81	18	24	12	—
	6	—	—	—	—	—	—	—	—
	7	—	—	—	—	—	—	—	—
B 0.1 ml. of mixture of = vol. of ARAN** and reaginic serum.	1	—	50	98	—	—	—	—	—
	2	—	—	—	—	—	—	—	—
	3	—	—	—	—	—	—	—	—
	4	—	—	—	—	—	—	—	—
	5	—	—	—	—	—	—	—	—
	6	—	—	—	—	—	—	—	—
	7	—	—	—	—	—	—	—	—
C 0.1 ml. of mixture of = vol. of normal rabbit serum and reaginic serum.	1	40	67	88	97	37	28	44	39
	2	24	36	74	—	—	—	26	—
	3	—	—	—	—	—	—	—	—
	4	—	—	—	—	—	—	—	—
	5	—	—	—	—	—	—	—	—
	6	—	—	—	—	—	—	—	—
	7	—	—	—	—	—	—	—	—
D 0.1 ml. ARAH***	1	—	44	60	63	—	—	—	—
	2	—	—	—	—	—	—	—	—

—no reaction.

*1=undiluted, 2=1:5, 3=1:10, 4=1:20; 5=1:80, 6=undiluted (controls — received saline instead of atopen), 7=no reaginic serum.

**Rabbit antiserum absorbed with normal human serum.

***Rabbit antiserum absorbed with homologous reaginic serum.

Table IV and in Figures 1 and 2. Figure 1 is a photograph of the reactions on one of the two recipients (D. H.) used in the experiment with reaginic serum X taken fifteen minutes after the injection of the atopen. (This recipient proved to be dermographic, which accounts for the erythema at sites 3 to 7 in Series B and C and at site 2 in Series D.) Figure 2 is a similar photograph of one of the two recipients (E. E.) used in the experiment with reaginic serum Y. The photographs that were taken of the reactions in the second recipient used with serum X and in the one used with serum Y did not differ materially from those in Figures 1 and 2, respectively. The appearance of the reactions was practically the same after thirty minutes in each recipient. Shortly thereafter, the wheals and erythemas gradually disappeared.

As may be seen from Table III, all four recipients gave positive reactions to the first five injections in Series A. In general, the size of the skin reactions diminished as the dilutions of the reaginic serum increased.

In series B, all the sites were negative when they were tested with short ragweed extract, except site 1 which was positive in both recipients (C. C. and D. H.) that received the mixture containing reaginic serum X undiluted. However, in recipient C. C. the reaction did not appear until the thirty-minute observation and in recipient D. H. the reaction at the fifteen-minute observation was weaker than that at site 1 in Series A, fading out by the time the thirty-minute observation was made. A possible explanation for the discrepancy in the reactions in site 1 between the two pairs of

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recipients may be that the antibody titer to reagin (as judged by the precipitin titer) was higher in the ARAN that was mixed with reaginic serum Y (12,800), than in the one that was mixed with reaginic serum X (6,400). Assuming that antibody to reagin was present in the ARAN it seems

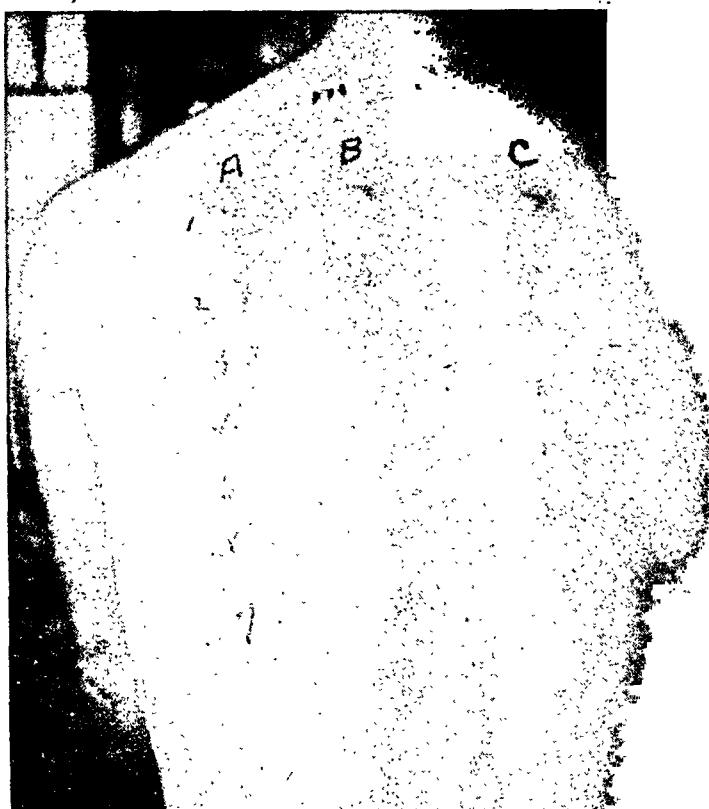


Fig. 1. Recipient D. H. injected with reaginic serum X taken fifteen minutes after the injection of short ragweed extract. For explanation of legends see Table III.

reasonable to expect that ARAN-Y would contain more anti-reagin antibody than ARAN-X, since the antiserum to reaginic serum Y had twice the precipitin titer of the antiserum to reaginic serum X. Therefore, ARAN-Y might be expected to neutralize more reagin than ARAN-X.

Contrary to expectations, the reactions in Series C did not parallel those in Series A. Positive reactions were observed only in site 1 of recipient E. E. and in sites 1 and 2 of the other three recipients. The sizes of these positive reactions were smaller, however, than those at corresponding sites in Series A, except for the reaction at site 1 in recipient N. S. Even in this recipient the reaction at site 2 (1:10) was smaller than the one at site 3 (1:10) in Series A. Apparently the normal rabbit serum had exercised an inhibitory effect on the Prausnit-Küstner reaction, especially where the higher dilutions of reaginic serum were used.

In Series D only sites 1 that had been injected with ARAH-Y were negative, while those that had been injected with ARAH-X were positive.

However, the reactions at sites 1 (Series D) that had been injected with ARAH-X were much smaller than those at the first four sites of Series A. In recipient C. C. the reaction was not observed until the thirty-minute reading. Furthermore, although the dilution of the reaginic serum in the

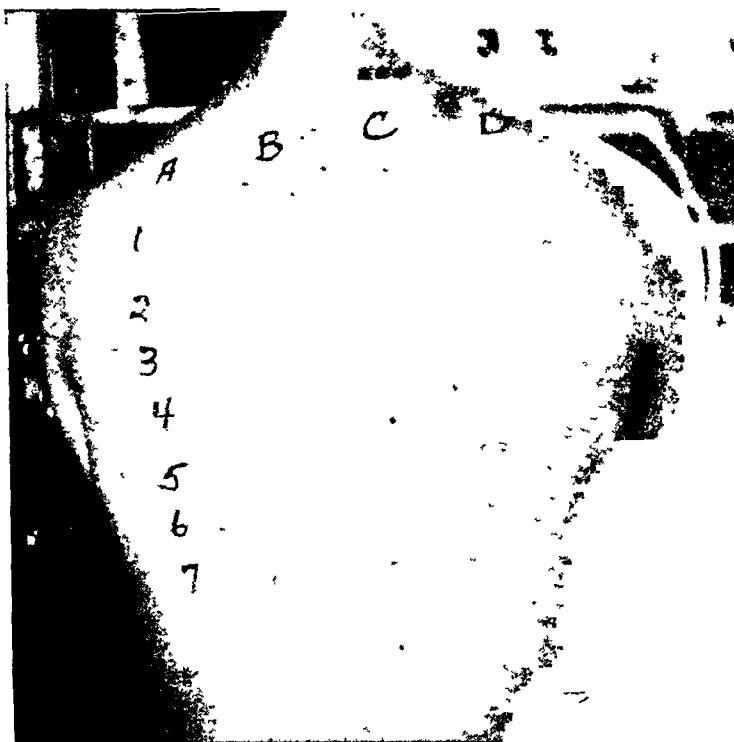


Fig. 2. Recipient E. E injected with reaginic serum Y taken fifteen minutes after the injection of short ragweed extract. For explanation of legends see Table III.

ARAH-X was 1:2 it did not elicit as strong a skin reaction as the 1:20 dilution of reaginic serum in Series A.

DISCUSSION AND SUMMARY

Although the results of this experiment are not clear cut, they appear to indicate the possible production of reagin neutralizing antibody in the two rabbits that were injected with sera that had been shown to possess reagin. In both of the recipients (E. E. and N. S.) that were injected intradermally with the rabbit antiserum that had been absorbed with normal human serum and then mixed with reaginic serum Y, no skin reactions were elicited when the specific atopen was injected (Series B). Nor was there any reaction in these recipients at the sites (1 in Series D) that received a primary injection of the rabbit antiserum that had been absorbed with the homologous reaginic serum when the specific atopen was injected. The evidence for the production of anti-reagin antibody against serum Y would be quite convincing were it not for the negative skin reactions observed at

all the sites in Series C except the first in recipient E. E. and the first and second in recipient N. S. when the atopen was injected after the sites had received initial injections of normal rabbit serum mixed with reaginic serum. Nevertheless, positive reactions did not occur at those sites in this series that were given initial injections of the normal rabbit serum mixed with undiluted reaginic serum (sites 1) or (in one recipient) with reaginic serum that had been diluted 1:5 (site 2), and not at corresponding sites (Series B) that received initial injections of the anti-serum that had been absorbed with normal human serum and then mixed with reaginic serum.

In the case of the two recipients (C. C. and D. H.) that received initial injections of the rabbit antiserum that had been absorbed with normal human serum and then mixed with reaginic serum X the results are less convincing. In both recipients a positive reaction occurred at site 1 in Series B, in one case (C. C.) not until the thirty-minute observation and in the other (D. H.) at the fifteen-minute observation only to disappear at the thirty-minute observation. Furthermore, although the amount of reaginic serum (undiluted) that was introduced into sites 1 in Series B was greater than that (1-5) which was injected into the control sites (2, Series A) the reactions at the former sites were smaller. The results with reaginic serum X at the sites that received primary injections of the rabbit antiserum (against serum X) that had been absorbed with reaginic serum X (Series D) were also unconvincing. The reactions at these sites in both recipients were positive upon the injection of the specific atopen. However, the reactions at both sites (1, Series D) were much smaller than even those at the control sites that received the reaginic serum alone diluted 1:20 (sites 4, Series A.) As with reaginic serum Y, not all the reactions at the control sites (that received initial injections of normal rabbit serum mixed with reaginic serum X) were positive. Only the first two sites were positive.

The results of this investigation are far from conclusive, but they do point to the possible presence of reagin neutralizing antibody in the two rabbit antisera used in the experiment, especially in the one against reaginic serum Y.

We had hoped to be able to carry out the investigation with a larger number of reaginic sera. Unfortunately, it was very difficult to obtain the co-operation of allergists in sending us the large amounts (at least 50 ml. per patient) of reaginic serum which we needed from untreated allergic patients. It is hoped that this preliminary report will serve to bring us larger numbers of samples for further studies.

ACKNOWLEDGMENTS

The authors are indebted to Dr. Kenneth P. Mathews of Ann Arbor, Michigan, and to Long Island College of Medicine, Brooklyn, New York, for the two reaginic sera, to Dr. Kenneth R. Andrews of Lexington, Kentucky, for the ragweed extract, and to Mr. George Scherr, of this department, for photographing the skin reactions.

(Continued on Page 291)

TREATMENT OF HAY FEVER WITH A COMBINATION OF A SYMPATHOMIMETIC AND AN ANTIHISTAMINIC DRUG

MARK H. MOTHERSILL, M.D., F.A.C.A.

Indianapolis, Indiana

EPHEDRINE is a sympathomimetic drug which was introduced about 1926 by Chen and Schmidt.¹ Until a few years ago ephedrine was probably more widely used for the symptomatic treatment of hay fever than any other compound. It was not perfect. Often it produced only partial relief, and efforts to increase the degree of relief by increasing the dose led to nervousness and wakefulness. The antihistaminic compounds which recently made their appearance were more effective in hay fever than ephedrine, and there was a tendency to replace ephedrine by antihistaminics in the symptomatic treatment of this disease. However, it seemed to us that instead of *substituting* antihistaminics for ephedrine it would be better to *combine* the two. The logic of such a combination is, first, that since both drugs are effective in hay fever, the combination might exert additive therapeutic action; and, second, that since antihistaminics as a rule produce sedation while ephedrine causes nervousness and wakefulness, these two side-effects might conceivably neutralize one another. There was also the possibility that the antihistaminics might potentiate the action of the sympathomimetic drugs.²

During the ragweed pollen season of 1948 we undertook a clinical comparison of twelve different preparations for the oral treatment of hay fever. Six of the twelve were antihistaminics, four were combinations of antihistaminics with sympathomimetics, one was a sympathomimetic alone, and one was a combination of an antihistaminic and a theophylline-containing compound. Approximately 100 patients who expected to have symptoms of ragweed pollinosis volunteered to take these drugs on successive days when they had symptoms and make reports on the relief and the side-effects. The work was done in the city of Indianapolis, which has higher ragweed pollen counts than most other cities in the country. This, we thought, might make the test more severe and the comparison more accurate.

The various drugs were prepared in white capsules so that their identity would not be known to the patients. They were numbered from 1 to 12 and were referred to throughout the season as "Drug No. 1," "Drug No. 2," et cetera. No one but the writer knew the identity of the preparations to which the various numbers referred. During the first week of August the patients were asked to come to the office and obtain their initial supply of drugs which consisted of eight envelopes numbered from 1 to 8. They also received instructions and a report blank. Each envelope contained what we thought would be an ample supply of capsules

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of that drug for one day's treatment. The patients were not to begin treatment until they developed symptoms of hay fever. Then they were to use capsules from Envelope No. 1 on the first day, from Envelope No. 2 on the second day, and so on. After having used each drug in the

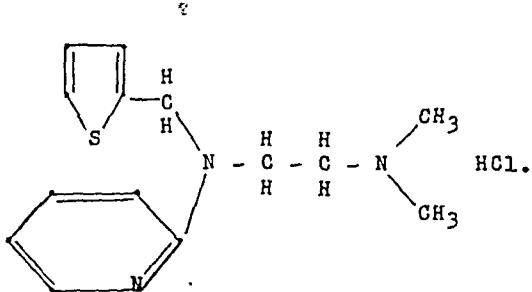


Fig. 1. Graphic formula of Histadyl.

series for one day, the patient was to start again with Drug No. 1 and go through the series a second time, omitting on this round any drugs that had proved unsatisfactory on the first. When the second round was finished, they began on the third round, provided they still had symptoms. On days when they had no symptoms they were to discontinue treatment. Incidentally, we observed that each patient seemed to have his or her own threshold pollen count above which symptoms developed. The threshold of one patient appeared to be a pollen count of less than ten. She began having symptoms during the first week of August and was still requiring treatment on September 30. Another patient had symptoms only for a week at the peak of the season.

At the end of each day's treatment the patients were to write on the report blank which we furnished them: (1) the date, (2) the number of the drug used that day, (3) the doses, (4) the degree of relief, and (5) the side effects. Once a week they were to present themselves at the hospital office with their written report of the previous week. At these visits questions were asked them in an effort to make interpretation of their report as accurate as possible, and they were then given another week's supply of drugs and another report blank.

When the season was completed, a large mass of data on twelve different preparations had been collected. Any effort to cover adequately the reports on the entire twelve would require a much longer paper than is here contemplated. Consequently, reports on only two of them, namely, Drug No. 3 and Drug No. 4, are being given. Drug No. 3 consisted of white capsules containing 25 mg. of Histadyl.* Drug No. 4 was also in white capsules of identical size and appearance and each capsule contained 25 mg. of Histadyl plus 8 mg. of Ephedrine Hydrochloride.

Histadyl is an antihistaminic drug which was investigated pharmacologically by Lee, Dinwiddie and Chen⁶ and by Landau and associates.^{4,5} Clinical studies were reported by Peirce,⁷ Feinberg,² and Gay³ and their

*Histadyl (Thenylpyramine, Lilly)

associates. Basically Histadyl is a dimethyléthylene diamine to which are attached pyridyl and thenyl groups (Fig. 1). It is supplied as the hydrochloride of this base.

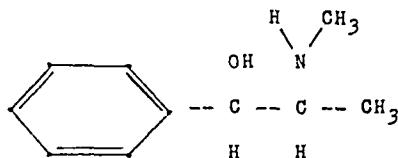


Fig. 2. Graphic formula of ephedrine.

DOSAGE

The dose was to be adjusted to the patient's requirements. The first dose of a drug which the patient had not taken previously was to be one capsule. If the relief obtained from this was insufficient and there were no side effects, the next dose was to be two capsules. If this gave incomplete relief and no side effects, the next dose could be three capsules, and so on. Later in the season when the patient took the same drug again he began the day with what had seemed to be the optimal dose previously. Toward the end of the season the dose was being adjusted more accurately and better results were being obtained. The doses varied from one to four capsules, the majority taking two capsules four to five times a day. In many instances the patient preferred to take two capsules with partial but satisfactory relief rather than to take three capsules and risk side effects. If side effects appeared without satisfactory relief, the patient was at liberty to discontinue further use of that number.

RESULTS

Originally 100 persons volunteered for treatment, but the number was reduced to sixty-seven for various reasons. Some of them were not sufficiently allergic to ragweed pollen to require treatment. In others the period of treatment was so brief that comparisons were impossible. Others found the task of following directions and making accurate reports too exacting.

In Table I it will be seen that the patients reported on a total of 145 treatment days with Histadyl and 147 treatment days with the combination of Histadyl and ephedrine. They were asked to report their results in five categories: (1) complete relief, (2) almost complete, (3) partial but satisfactory, (4) very little relief, and (5) no relief.

The sum of the first three categories, which would include all who obtained enough relief to call it satisfactory, was 87 per cent for Histadyl and 90 per cent for the combination. The incidence of complete and almost complete relief was 36 per cent for Histadyl and 48 per cent for the combination of Histadyl and ephedrine.

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**TABLE I. SUMMARY SHOWING DEGREE OF RELIEF
IN THE TREATMENT OF RAGWEED POLLINOSIS**

Degree of Relief	Histadyl		Histadyl, 25 mg., and Ephedrine Hydrochloride, 8 mg.	
	Number of Treatment Days	Per Cent of 145	Number of Treatment Days	Per Cent of 147
Complete	41	28%	63	43%
Almost complete	12	8%	8	4%
Fair to good	73	51%	61	41%
Very little	3	2%	3	2%
None	16	11%	12	8%
Total	145		147	
Relief ranging from fair to complete including almost complete and complete	126	87%	132	90%
	53	36%	71	48%

SIDE EFFECTS

In the report blanks there was a column headed "Side effects." The patients were asked either to write "none" in this column or to describe the side effect, if any. The necessity of writing something in the column may have caused them to record a few discomforts which were trivial and a few that were coincidental. In Table II the side effects are listed in the language used by the patient in describing them. This table may aid in giving an insight into the nature and degree of the symptoms. Totals of thirty-four side effects for 145 treatment days with Histadyl and thirty-two side effects for 147 treatment days with the combination were reported. It will be seen that the percentage of patients having side effects with the combination was only slightly lower than with Histadyl alone. Qualitatively, however, the side effects were different.

In Table III the side effects are classified into six groups. The incidence of sedation was 15 per cent with Histadyl and 9 per cent for the combination. Nervousness, insomnia, and headache are grouped together because they are characteristic side effects of ephedrine. The incidence of these three was 2 per cent following Histadyl and 7 per cent following the combination.

DISCUSSION

This is a clinical rather than a pharmacological study. Pharmacologists have been of great value in advancing our knowledge of antihistaminic compounds, but any effort to predict from pharmacological figures which of two compounds will constitute the most satisfactory clinical treatment of hay fever is likely to be misleading. Men have many similarities to mice, but men are *not* mice. Hence the clinical test, particularly for a drug used as symptomatic treatment, is a more nearly final answer.

The incidence of sedation was reduced from 15 per cent to 9 per cent when the combination of Histadyl and ephedrine was used, but the incidence of nervousness, insomnia, and headache was increased from 2

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TABLE II. SIDE EFFECTS IN THE LANGUAGE OF THE PATIENT

Symptoms	Number Reported with Histadyl	Number With Histadyl and Ephedrine
Slightly drowsy	3	3
Drowsy	16	9
Sleepy	3	0
Tired	0	1
Dopy	1	0
Slight headache	1	2
Headache	1	3
Slightly nervous	0	1
Nervous	1	1
"A little shaky"	0	1
Jittery	0	1
Could not sleep	0	1
Slight dizziness	0	2
Dizzy	3	1
Dryness of mouth	4	2
Nausea	0	1
Indigestion	0	1
Cramps?*	0	1
Diarrhea	1	0
Fever	0	1
TOTAL	34	32

*The patient herself inserted the question mark.

TABLE III. CLASSIFICATION OF THE REPORTS ON SIDE-EFFECTS

Type of Side Effect	Histadyl		Histadyl and Ephedrine	
	Number	Per Cent of 145	Number	Per Cent of 147
Sedation	23	15%	13	9%
Headache, nervousness, or insomnia	3	2%	10	7%
Dizziness	3	2%	3	2%
Dryness of mouth	4	3%	2	1%
Gastrointestinal symptoms	1	1—%	3	2%
Fever	0	0	1	1—%
Total	34	23%	32	21%

per cent to 7 per cent. A study of the patients' descriptions indicates that, as a rule, the side effects were not very severe.

Some individuals appear to be excessively responsive to stimulation by sympathomimetic drugs. As stated earlier, a total of twelve drugs were included in this study and five of them contained sympathomimetics. One of our patients picked out these five and suspected that each of them contained ephedrine because each one gave him a headache. The number of patients overresponsive to ephedrine was small, and these were better satisfied with Histadyl alone. The majority were better pleased with the combination.

SUMMARY

1. During the ragweed hay fever season of 1948 a group of sixty-seven patients reported on 145 treatment days with Histadyl and 147 treatment days with capsules containing 25 mg. of Histadyl and 8 mg. of Ephedrine Hydrochloride.

2. The two preparations were supplied in white capsules of identical appearance.

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3. The incidence of satisfactory relief, ranging from fair to complete, was 87 per cent for Histadyl and 90 per cent for the combination.
4. The incidence of complete or almost complete relief was 33 per cent higher for the combination than for the antihistaminic alone.
5. The incidence of side effects classified as sedation was 15 per cent with Histadyl and 9 per cent with the combination.
6. The total incidence of nervousness, headache, and insomnia was 2 per cent during Histadyl therapy and 7 per cent when the combination was being given.
7. The majority of patients were better pleased with the combination.

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COMPARATIVE STUDIES OF CERTAIN ANTIHISTAMINE DRUGS

N. B. DREYER
Burlington, Vermont

IT is too commonly believed that histamine stimulates all smooth muscle. Experience shows that there are many exceptions to this generalization; for example, the elasmobranch intestine, mesentery, and uterus are completely unaffected by histamine. In contrast the teleost is very sensitive to histamine. In mammals there are wide variations in sensitivity. The white mouse and the rat are most refractory, whereas the guinea pig is most susceptible. Even within a mammalian species, the actions of histamine vary. These actions may be classified as motor, inhibitory, and secretory. In the human and the guinea pig, the uterus is stimulated to powerful contraction. The rat uterus, on the contrary, is relaxed by histamine. In mammals, with the exception of the guinea pig, the large intestine contracts more readily in response to histamine than the small intestine. Among the inhibitory effects are the arteriolar and capillary dilatation which cause the histamine wheal and flare in the skin and vasodepression. Its secretory effects are best illustrated by an increased gastric secretion. Following intra-arterial injection in carnivora, salivary secretion is stimulated.

The antihistamine drugs do not diminish or abolish with equal ease all of these various actions of histamine. They exert no influence on the gastric secretion by histamine, and while they do inhibit the histamine wheal and flare when applied locally, they do not do so completely when given orally. It is now generally agreed that these drugs compete with histamine at effector sites in accordance with the Langmuir adsorption isotherm.⁵

It should be emphasized that antihistamine drugs are different chemical substances which exhibit different pharmacological and clinical properties. To illustrate these differences, it may be noted that some of these drugs possess local anesthetic properties; they have atropine-like, antispasmodic, quinidine-like, Demerol-like, and musculotropic actions. And finally, some antihistamines sensitize to epinephrine while others desensitize.

The antihistamines have dual actions on some tissues as shown by their effects on striated muscle. In small concentrations, there is increased contraction due to indirect (nerve) stimulation. In high concentrations, indirect stimulation is suppressed, presumably because of block at the myoneural junction, but contraction is not inhibited upon direct stimulation of the muscle. Similarly, the antihistamines depress impulse transmission at autonomic ganglia. In the autonomic system, cholinergic responses are partially or completely depressed, depending upon the drug used, whereas adrenergic responses are usually undiminished and may even be potentiated with some drugs.

From the Department of Pharmacology, School of Medicine, University of Vermont.

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Other dual actions are observed with the antihistamines; for example, Neoheptramine and Neo-Antergan in small doses depress intestinal motility, but in large doses they stimulate. Other drugs stimulate motility in small doses, but depress in large doses. Similarly, a dual effect on the blood pressure may be demonstrated with Trimeton and Neo-Antergan. Small

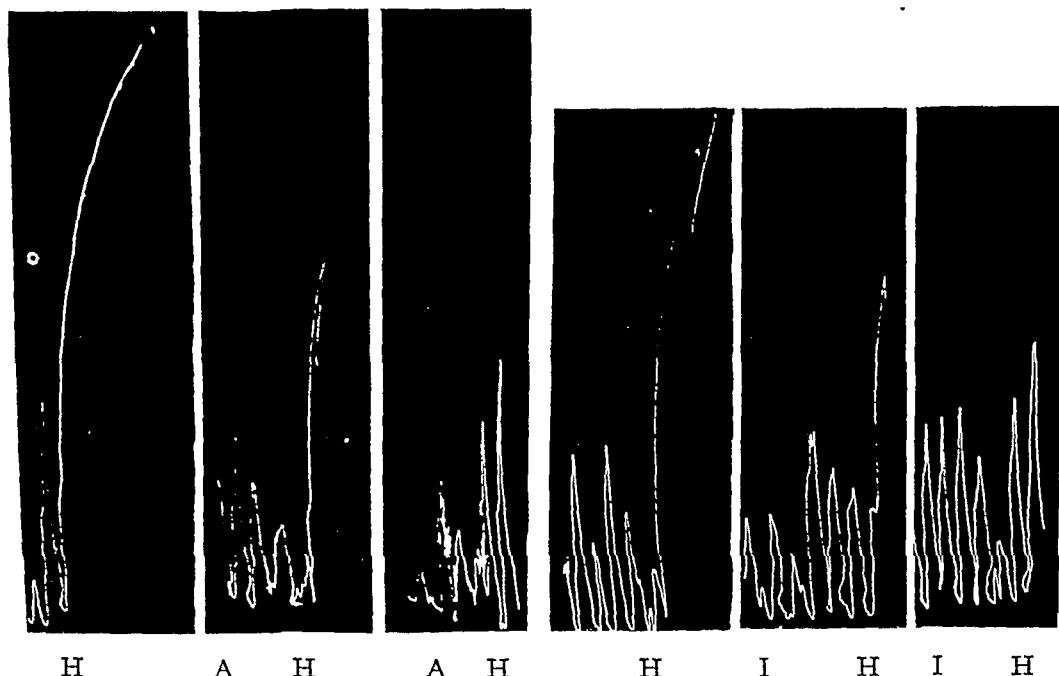


Fig. 1. Guinea pig uterus. Comparison of Anahist (A) and Inhiston (I) at concentrations of 1.8 and 3.6 mcgm. Histamine (H) at .2 mcgm. added to bath.

doses of these drugs cause a brief hypertension, but large doses cause vasodepression.

Recently, several antihistamine drugs were made available to the public without a prescription. Because of the limited pharmacological data reported, and since these drugs will now be used extensively in industrial medicine to reduce absenteeism due to the common cold, and since the drugs will be used by the public without medical supervision, it seemed desirable to compare some of the over-the-counter antihistamines.

Guinea Pig Ileum.—Tissues were suspended in a 30 c.c. bath of oxygenated Ringer-Locke solution at 37° C. Following the addition of histamine in amounts sufficient to evoke a sub-maximal response (0.5 to 4.0 micrograms per 30 c.c. bath fluid), the concentrations of Anahist and Inhiston required to counteract the histamine contraction were determined. The results with Anahist were the same as those previously reported.¹ Careful evaluation of Inhiston failed to reveal any difference in potency as compared with Anahist.

Guinea Pig Uterus.—Similarly studied on the isolated guinea pig uterus, both drugs again appeared to be equal in activity (Fig. 1).

Excised Tracheal Tissue.—Studied according to the method of Castillo and deBeer,¹ as described earlier,⁴ both drugs at concentrations of .02 micrograms per c.c. of bath fluid produced a 26 to 27 per cent reduction of the histamine contraction. Here, again, no difference in activity was observed.

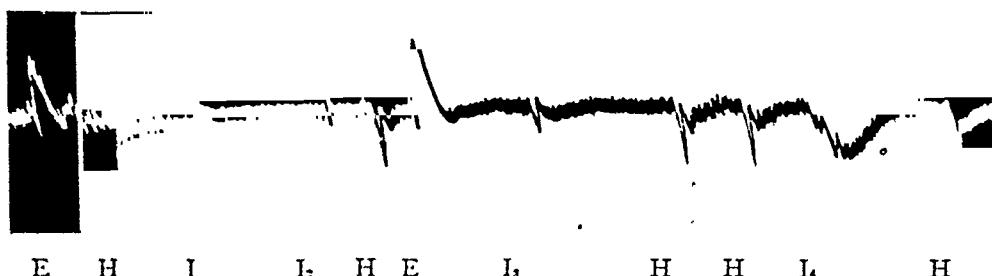


Fig. 2. Dog—nembutal anesthesia, atropinized. Shows the potentiation of epinephrine (E), 2 ug. per kg. response following Inhiston (I) and the failure of Inhiston to abolish the hypotensive effects of .75 ug. per kg. of histamine (H). At I₄ 9.5 mg. per kg. of Inhiston reduced but did not abolish the hypotensive effect of .75 ug. per kg. of histamine.



Fig. 3. Dog—nembutal anesthesia, atropinized. Shows the depression of the epinephrine (E) 2 ug. per kg. response following Anahist (A) and the increase in the epinephrine response following Inhiston (I) 5 mg. per kg. in spite of the presence of Anahist. Both Anahist and Inhiston diminished but did not abolish the hypotensive effect of .6 ug. per kg. of histamine (H).

Blood Pressure.—The potencies of both drugs in counteracting the effect of intravenous histamine were determined in atropinized dogs under sodium pentobarbital (30 mg. per kilo i.v.). At doses of 0.1 to 0.3 micrograms of histamine per kilo, both drugs appeared equally effective in abolishing the histamine vasodepression. At higher doses of histamine (0.5 to 1.0 mcg. per kilo, the vasodepression was never completely abolished by either drug (Figs. 2 and 3).

Capillary Permeability.—Recently, Lovejoy, Feinberg, and Canterbury³ reported a capillary wheal-flare test. They believe that their test results parallel the clinical activity of antihistamine drugs. In view of their findings, the action of Anahist and Inhiston upon histamine-induced capillary permeability was studied intracutaneously in rabbits. Using the ex-

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perimental design previously reported,⁴ Anahist was found to be about twice as effective as the other drug.

Acute Toxicity.—Determined in the C. F. 1 strain of mice, the LD₅₀ in mg. per kilo i.p. was found to be 96 for Inhiston (94-107 per cent limits of error), and 116 (93-108 per cent) for Anahist. In this test, the former appears to be significantly more toxic than Anahist.

Given the activity and the toxicity of a drug, one may compute a therapeutic index as the LD₅₀ divided by the effective dose—50. It is evident from the foregoing data that Anahist would enjoy the better therapeutic index, since it is equal to or more active than Inhiston and less toxic. No attempt has been made to calculate therapeutic indices because they are not applicable to man and cannot be carried over to clinical practice. The recent advertising claims made on the basis of this time-honored laboratory statistic are misleading. Such use of the therapeutic index is to be regretted.

Blood Pressure Studies.—Anahist, in small or large doses, produces a hypotension of short duration. Inhiston, in small doses (up to 1 mg. per kilo), produces a slight hypertension without any increase in pulse rate in the atropinized or unatropinized animal. At the usual rates of injection, larger doses of this drug (2.5 to 5 mg. per kilo) cause a more prolonged fall in blood pressure than that produced by comparable doses of Anahist. This prolonged vasodepression may be due to an Inhiston depression of the myocardium.

It has been reported that Pyribenzamine and other antihistaminics enhance epinephrine responses² while Anahist does not.⁴ In the present study, it was found that Inhiston in concentration of 0.5 to 2.5 mg. per kilo potentiates epinephrine (Fig 2). In contrast, epinephrine responses following Anahist were always diminished (Fig. 3). These results suggest that Anahist may more safely be used in hypertensive states.

Isolated Frog Heart.—In small concentration (1 microgram per c.c.), neither drug affected the Straub frog heart preparation. Larger concentrations (5 to 10 micrograms per c.c.), of both drugs caused an equal and well-marked diminution in systolic contraction. This action disappeared following changes of Ringer solution.

Isolated Guinea Pig Heart.—Langendorf perfusion of 50 micrograms of Anahist caused myocardial depression with recovery. There was no change in coronary flow or heart rate. In the same preparation, 50 micrograms of Inhiston produced a more pronounced depression with a much slower recovery in amplitude (Fig. 4).

Cat Intestine In Situ.—Intravenous injections of the drugs (0.1-0.5 mg. per kilo), in anesthetized cats (Chloralose 100 mgs. per kilo) produced

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contrasting responses. As found earlier,⁴ Anahist in small doses produced a depression of intestinal motility with recovery. Higher doses produced stimulation. Inhiston had a slight stimulant effect in small doses, while larger doses produced a prolonged depression. This depression of the gut can be counteracted by larger amounts of Anahist.

Fig. 4. Perfused guinea pig heart—Langendorff preparation. Depression of heart contractions with equal amounts of Inhiston 25 mg. and Anahist Ulen (50 mgm. added to perfusion fluid).

Persistence—Male guinea pigs (300 to 400 gm.) were given 50 mg./kg. of Anahist, Inhiston, and Chlor-Trimeton orally. The Chlor compound was included because of structural similarity and because it has recently been presented to the medical profession. At varying time intervals after administration of the drugs, a lethal dose of histamine (0.5 mg./kg. as base) was injected intravenously, and survival was taken to indicate the persistence of the drug in the animal. Judged in this way, Anahist remained in the animal for less than eight hours. This persistence is in keeping with clinically-accepted dosing schedules. Inhiston persisted in the animal for more than twenty-four hours, indicating that this drug will accumulate following repeated doses. The Chlor compound persisted for more than forty hours, indicating cumulation and the risk of possible organ pathology.

Repeating the experiment with a smaller dose (5 mg./kg.), animals were protected for shorter periods of time, but the same over-all picture obtained. The Chlor compound was the most persistent, Inhiston less persistent, and Anahist was the least persistent.

The persistence of these drugs was also determined in nephrectomized dogs under sodium pentobarbital (30 mg./kg.) by the ability of these drugs to counteract the vasodepression of intravenous histamine. Judged in this way, the persistence of the three drugs was essentially the same as described in the preceding experiments.

SUMMARY

It seems clear from the foregoing experiments and from the bulk of published evidence that the various antihistamine compounds are different

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WHAT IS TO BE OUR BASIC PROFESSIONAL RELATIONSHIP?

CARL R. ROGERS, Ph.D.

Chicago, Illinois

IT IS a very unusual experience for me to be invited to speak to a conference of allergists. I have no special knowledge of allergic conditions and no close knowledge of the problems the physician faces in dealing with these problems. In fact, insofar as the field of allergy treatment is concerned, I would like to make it clear at the outset that I have no experience in that realm, and nothing to offer to this group except that which arises out of the experience that I and my colleagues have had in attempting to deal with psychological problems. Since you, too, are dealing with syndromes which often have a large psychological component, it may be that we can find here an area upon which we can fruitfully think together. The phase of that area which I have chosen to discuss is the basic question as to what constitutes the most effective relationship with our patients or clients—the relationship from which they can obtain maximal help.

I should like first to say a few words about the relationship of the physician and patient in those situations which are clearly and almost solely organic. I realize that when an outsider tries to describe a profession he is apt to misrepresent it, and if I misrepresent this relationship I trust it will be brought out in the discussion. It seems to me that the element of primary importance in the physician-patient relationship in those situations where the problem is organic is the element of accurate evaluation of the patient by the physician. The physician, the expert, must adequately gather the data through history-taking, through physical examination, through laboratory tests. He makes his tentative interpretations and evaluations, checking these evaluations against further tests. The primary responsibility for the processes of diagnosis and treatment lies in the hands of the physician. The locus of evaluation resides primarily in him. He is continually asking himself such questions as: What does this sign mean? How shall I evaluate this symptom? What is my judgment of all the interrelated observations? In all of this process it is secondary or even immaterial whether the patient has any basic understanding of the illness or of the process of cure. The effectiveness of the relationship rests basically upon what goes on in the mind of the physician.

In dealing with organic disease and dysfunction this mode of approach has been so successful that one might say that the progress of medicine has been measured by the development of new evaluation procedures. The physician, with the aid of an increasing array of technicians, has learned how to make more accurate, more discriminating, and more complex eval-

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ations. The more expert he has become in these judgments, the more he has been able to cope with the organic problems which his patients present.

With this impressive record of success, it has quite naturally been assumed that progress in dealing with psychological problems would follow the same pathway. Clinical psychologists and psychiatrists alike have tended to assume that if they could understand, diagnose and evaluate psychological conflicts and deviations with an accuracy equal to the physician's evaluations of organic conditions, then treatment of these psychic difficulties would be equally effective. Hence the enormous development, in both the psychological and psychiatric fields, of systems of classification of mental disorders, of complex methods of psychological measurement and diagnosis, and a great concern with the discovery of basic causes of conflict. I will not bore you with a detailed description of these developments.

On the whole this type of development has been disappointing, at least insofar as therapy is concerned. Many facets of human nature have been discovered, measured and classified, but effective help to the person has not necessarily resulted. The difficulties which have arisen seem to me to point up the difference between dealing with organic and psychological problems. I would describe the difficulties in these terms:

1. It has gradually come to be recognized that in psychological conflicts, improvement or cure can only come about through the individual learning for himself the causes of his behavior and learning for himself new ways of perceiving and reacting to these causes. If, in a particular neurosis, I know very accurately that the client's irrational reactions are due to a very strict early environment, and the introjection of perfectionist standards, with a consequent development of feelings of unworthiness and a repression of most of her spontaneous emotional reactions, all this knowledge on my part is of no help to my client. And if I should attempt to teach her this diagnosis, every therapist knows that an increased defensiveness would be the most likely result. As professional workers we have painfully realized that accurate evaluation in the mind of the expert is of practically no help to the client, in situations of psychological conflict and difficulty.

2. A second difficulty which has less frequently been commented upon is that there is some evidence that in situations of psychological difficulty, the very process of being evaluated by the expert is in itself detrimental rather than therapeutic. The person who has been informed, accurately enough, that he is a compulsive, or a rejecting parent, or that he has average intelligence, tends to lose, to a certain degree, his basic confidence in himself. Essentially he comes to feel that he cannot know himself, that only the expert can adequately evaluate him. Yet to damage his confidence in his ability to evaluate himself and his experience is to damage the very foundation upon which therapy must rest.

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3. Still another difficulty lies in the fact that as psychotherapy spreads to an increasing number of people, certain philosophical questions come to assume greater importance. If, as the expert, I evaluate the strengths and weaknesses of this man's job relationship, marital relationship, and personal behavior, understand the causes of his difficulties, and set goals for his therapy, then almost inevitably I find myself choosing his values, or influencing his own choice of values. Shall he adjust to the status quo of his work situation or try to change it? Will therapy consist of his working out a better relationship with his wife or divorcing her? Is his behavior healthy or should I aim to change it? As I see it, insofar as we set for ourselves any such goals in therapy we enter the realm of values, and to a certain extent set ourselves up as arbiters of what is right. In a recent article which shocked some of my professional colleagues, I tried to spell out the implication of this point of view as I see it: that if it is accepted as sound, its eventual working out in the social milieu involves a basic philosophy of the control of the many by the self-selected few. I will not, however, belabor that point here.

What I am trying to point out thus far could be summarized by saying that a physician-patient relationship in which the role of the expert is to make accurate evaluation has been highly effective in dealing with organic problems; that it has been entirely natural that professional workers have assumed that the same approach would be equally effective in dealing with psychological problems; that experience seems to be indicating that actually it falls short in effectiveness in dealing with psychological conflict, that it may even be detrimental to treatment of the individual, and that it raises certain disturbing philosophical questions which cannot be lightly disregarded.

But if this type of relationship does not seem to provide the best mode of dealing with psychogenic problems, what is the alternative? Here it seems to me that most effective psychotherapies have been moving toward a different sort of relationship with the client or patient, and that client-centered psychotherapy has perhaps stated this relationship in its most extreme form. Whether it is the correct description of the effective relationship, only time and further experience and research can tell.

The sharp difference between the client-centered orientation and the physician-patient relationship we have been describing lies in the locus of evaluation. Rather than regarding the therapist as the evaluator, it is the client who is given the opportunity to evaluate, at deeper and deeper levels, the meaning and the significance of his behavior and his feelings. The responsibility rests in the client's hands for choosing whether to explore certain feelings or to leave them untouched, whether to proceed at a rapid rate of explanation or a slow one; it is his responsibility to discover the hidden relationships in his experience which we call insight; it is his responsibility to determine the way he will behave in the light of his new understandings. The responsibility of the expert lies in the difficult

and complex and emotionally demanding task of creating a psychological atmosphere in which the client can undertake this exploration and re-evaluation of self. The role of the expert is to create a relationship of such acceptance, understanding, warmth and respect that the individual feels safe from threat, and is freed to explore and understand those elements of his behavior and of himself which he has not understood.

As our practice of such a point of view has extended, as we have utilized it in dealing with a wider range of problems, the basic hypothesis upon which it rests has become evident with increasing clarity. This hypothesis is that the individual has within himself the capacity, latent if not evident, to understand those aspects of his life and of himself which are causing him unhappiness or stress or pain, and the capacity and the tendency to reorganize himself and his relationship to life in the direction of a socialized maturity, in such a way as to bring a greater degree of internal comfort. It is an hypothesis that the individual has a sufficient capacity to cope with life if a psychological atmosphere suitable for personal growth can be provided.

How does this sort of hypothesis work out in practice? In what way does the therapist create the atmosphere of which we have spoken? In what way does the client react? What is the process by which help is achieved? Much has been said and written about this, and a very brief description is likely to be misleading. Yet I shall try to put in a few words an account of the conditions which the therapist endeavors to create, and the process which is facilitated in the client.

1. Therapy seems most likely to occur when the therapist feels, very genuinely and deeply, a warm attitude of acceptance of and respect for the client *as he is*, with the potentialities inherent in his present state. This means a respect for the attitudes which the client now has, and a continuing acceptance of the attitudes of the moment, whether they veer in the direction of despair, or toward constructive courage, or toward a confused ambivalence. This acceptance is probably possible only for the therapist who has integrated into his own philosophy a deep conviction as to the right of the individual to self-direction and self-determination.

2. A second and corollary condition making for therapy is the complete willingness of the therapist for the center or locus of evaluation and responsibility to remain with the client. All judgments, all evaluations, all changes in evaluations, are left to the client. The counselor not only avoids voicing any evaluations of the client, or his behavior, or the meaning of his behavior, or the behavior of others—but by his immersion in the empathic process, tends to avoid *making* these judgments. Likewise responsibility is left with the client—whether it be responsibility for choosing the next topic of his conversation, or responsibility for some grave choice. This whole attitude on the part of the therapist is, if it is to be

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effective, real and not forced. It is a basic willingness to help the client realize his own life in his own terms, and an unwillingness to attempt to take over the responsibility for his life or any part of it.

3. A third condition for therapy is the therapist's willingness and sensitive ability to understand the client's thoughts, feelings, and struggles, from the client's point of view. This ability to see completely through the client's eyes—to adopt his frame of reference—has seemed to be an important way of implementing the fundamental hypothesis, and is the basis for the use of the term "client-centered."

4. A fourth condition of therapy is that the counselor use only those techniques which implement these basic attitudes. Techniques are definitely secondary to attitudes, and seemingly poor technique may succeed if attitudes are sound, while we have not found the reverse to hold true. The most helpful techniques have seemed to be those which communicate something of the attitudes which the therapist deeply holds—his acceptance of the person as he is at this moment, and his empathic understanding of the client's attitudes as seen from the client's point of view.

These would seem to us to be the ways in which the therapist carries out his basic hypothesis. In one sense all of these conditions are wrongly described, since it is the experiencing of these by the client which is significant for therapy. It could be more truly stated that the conditions of therapy are met when the client experiences the respect and acceptance the therapist has for him, experiences an empathic understanding, experiences the locus of evaluation as residing within himself, experiences no significant limitation on the expression of his attitudes. I have chosen however to describe the situation as the counselor perceives it.

When the therapist is successful in establishing these conditions, what is the process which is experienced by the client? I can only touch very briefly upon the most common characteristics of a rich and complex process.

In the first place the client rather quickly comes to experience this process as centered in him. He recognizes, in a way which comes to have more and more meaning, that he is working on himself. As one client puts it, "In counseling we were mostly *me* working on my situation as I found it. . . . I was the one that mattered, my thinking was the thing that was important, and my counselor was almost a part of me working on my problem as I wanted to work on it."

Another aspect of this process of therapy is the client's experience of exploration of attitudes, feelings, and perceptions. He tends first to talk about his symptoms, or about others, or about his environment. But as he feels the safety of the relationship, and recognizes that all his attitudes are accepted and understood, without evaluation of any kind, he finds himself talking more and more about himself. He also tends in the direc-

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tion of discussing those experiences which do not seem to be a part of himself—experiences which he has not “owned” or which he has denied to awareness. Thus, in general, there is evidence that this exploration tends to go from symptoms to self, from others to self, from surface concerns to deeper concerns, from conscious feelings regarding self to feelings and experiences which have been denied to awareness because they are inconsistent with the self as it is organized.

As this exploration of self continues, he can, in the safety of the relationship, bring up and look at and perceive clearly, some of the feelings he has denied. This is a fearful and frightening part of the process, the degree of fear depending upon the degree of discrepancy between the attitudes he has consciously held and the feelings he has been denying. Seeing the relationship between these denied attitudes and his behavior is what may be thought of as insight.

As he recognizes more freely all the attitudes and experiences he has had, he finds himself reorganizing himself on the basis of these new perceptions. He can be himself more fully, in terms of these newly accepted perceptions. He finds his behavior moving in new directions which are consistent with this new idea of himself. He finds that he now has sufficient understanding and control of himself to free himself from the therapist and to move out on his own.

This is a bare outline of the process as we have seen it many times. Perhaps a very brief example may bring the outline to life. The wife of a lawyer came to the Counseling Center for help with an embarrassing physical symptom which seemed to crop up most frequently in situations where it would cause her and her husband the greatest degree of humiliation. Physicians could find no organic cause. At first she talked only of the symptom and its occurrences. She was very inhibited, stating that she wasn't sure she even had any feelings. She stressed that the symptom could have no relationship to her husband or the fact that she did not feel much liking for her oldest child. Little by painful little, she tentatively explored her desire to get her own way, her need to oppose her husband at times and her fear of doing so openly. She finally formulated for herself—first tentatively and then with assurance—the fact that the symptom was a way of attacking and humiliating her husband, and at the same time punishing herself for wanting to attack him. She could accept herself as a “stubborn wench” who held these attitudes. She recognized that she could not hold in her occasional antagonisms to her husband, but must find new channels for their expression. “After all, a temper tantrum would be better than this symptom” was her way of putting it. The symptom lost its uncontrollable force, and she was able to give up therapy, having made much improvement. Here we can see, in brief, the different elements of the process as I have described it: the recognition that this is a place where she can work on herself, the process of exploration which

(Continued on Page 286)

BLOOD LEVELS INDUCED BY PENICILLIN-ANTIHISTAMINE PREPARATIONS

F. J. MURRAY, BARBARA TAYLOR and MILTON J. FOTER
Cincinnati, Ohio

A VAST literature has accumulated on the subject of penicillin sensitivity and an excellent review of papers published up to October, 1948, is available.² This review deals with toxicity as well as sensitivity reactions.

From the evidence cited in the literature it is obvious that penicillin reactions occur most frequently in individuals who have had several courses of the antibiotic. Skin tests have been found unreliable in predicting the occurrence of reactions. The incidence and severity of such reactions has not been greater in allergic individuals than in non-allergic individuals.¹

Twelve types of reaction have been reported following administration of penicillin and the over-all incidence of reactions has been reported at 2 to 5 per cent.¹

With the variety of penicillin forms available and with the variations from lot to lot or from manufacturer to manufacturer, it has been stated that no clear-cut method of treatment is applicable to all patients.²

Brown² has concluded that the results of antihistaminic therapy are variable; others have indicated favorable results.^{4,5,7} On the basis of the favorable reports Simon has reasoned that an antihistaminic should be of much greater value in preventing penicillin reactions.⁸

Using the antihistaminic Decaprym* (doxylamine) Succinate (dimethylaminoethoxy-methylbenzylpyridine), since he had found it to be the drug of choice in treatment of reactions, Simon concluded from his studies that the antihistaminic in combination with penicillin resulted in much fewer reactions, was practically painless on injection, and evoked blood levels comparable to those produced by penicillin alone.

Since Simon's work was carried out with crystalline potassium penicillin G aqueous with a Decaprym Succinate solution, it was thought desirable to study rabbit blood levels with other forms of penicillin preparations. The local anesthetic action of Decaprym was an apparent advantage in that it lessened pain of injection, but it was necessary to demonstrate that the advantage was not offset by reduced blood levels. The purpose of this paper is to show the effect, or lack of effect, of Decaprym on blood levels induced by various pharmaceutical forms of penicillin.

METHOD AND RESULTS

The dosage of penicillin administered to rabbits in these studies has been either 30,000 or 40,000 units per kilogram of body weight, the larger dose

From the Department of Bacteriology, Research Laboratories, The Wm. S. Merrell Company, Cincinnati, Ohio.

*Reg. Trade Mark of The Wm. S. Merrell Company.

Presented at the Sixth Annual Meeting of The American College of Allergists, January 15-18, 1950, St. Louis, Missouri.

BLOOD LEVELS—MURRAY ET AL

TABLE I. COMPARATIVE PENICILLIN SERUM LEVELS
 Decapryn-Potassium Penicillin G in Oil—2% AL, Monostearate and Potassium
 Penicillin G in Oil and Beeswax (Romansky)

Sample	Rabbit	Hours—Units per cc.				
		1/2	1	3	6	24
Penicillin in Oil with 10 mg. Decapryn Base, per cc.	1	1.7	1.2	2.1	0.50	0
	3	9.0	6.4	2.6	0.19	0
	5	10.0	7.8	0.74	0.10	0
	7	6.7	5.6	2.6	1.50	0
	9	11.0	6.8	2.7	0.19	0
	11	2.0	7.0	2.8	0.92	0
	13	1.5	5.6	1.1	0.10	0
	15	6.5	10.0	1.4	0.35	0
	Median	6.6	6.6	2.5	0.27	0
	2	5.5	9.5	1.8	0.70	0.04
Penicillin Control (Romansky Formula)	3	7.2	8.0	1.3	0.35	0
	6	10.5	7.4	1.6	0.26	0
	8	5.0	5.9	0.59	0.15	0
	10	6.5	7.4	0.70	0.10	0
	12	7.5	7.6	1.0	0.34	0
	11	8.0	7.4	2.4	0.42	0
	16	11.5	3.2	0.82	0.23	0
	Median	7.4	7.4	1.2	0.30	0

TABLE II. COMPARATIVE PENICILLIN SERUM LEVELS
 Potassium Penicillin G with and without Saline Decapryn Diluent

Sample	Rabbit	Hours—Units per cc.			
		1/2	1 3	6	24
Penicillin* with 5 mg. Decapryn succinate per cc.	2	10.5	0.4	0	0
	4	27.7	2.2	—	0
	6	22.5	0.9	Dead	—
	8	20.5	1.6	0.07	0
	10	27.7	3.1	0.25	0
	12	21.0	1.0	0.06	0
	14	27.7	3.3	0.42	0
	16	27.7	1.6	0.18	0
	Median	25.1	1.6	0.12	0
	1	19.5	0.38	0	0
Penicillin* Control	3	27.0	10.50	0	0
	5	26.2	1.20	0	0
	7	27.7	0.42	0.19	0
	9	25.5	2.00	0.05	0
	11	30.0	0.50	0.04	0
	13	28.5	1.20	0	0
	15	27.7	1.30	0	0
Median		27.3	1.20	0	0

*Peni-Cry-stin Trademark of The Wm. S. Merrell Co.

being employed for the fortified preparations. This dosage is based on a report that the percentage of animals showing concentrations of penicillin in the serum in excess of 0.05 units per c.c. following such dosage will equal the per cent of patients showing concentrations of penicillin equal to, or greater than, 0.03 units per c.c. following the injection of 1 c.c. (300,000, or 400,000 units) of the same preparation.⁶

All rabbit injections were made in the posterior left thigh muscle and all bleedings were by intracardial puncture. The assay method employed was the *Sarcina lutea* blood penicillin assay.³ The average weight of the rabbits used was approximately 2.6 kilograms.

BLOOD LEVELS—MURRAY ET AL

TABLE III. COMPARATIVE PENICILLIN SERUM LEVELS
Decapryl-Procaine Penicillin G and
Procaine Penicillin G for Aqueous Injection

Sample	Rabbit	Hours—Units per cc.		
		½	6	24
Procaine Penicillin* with Decapryl Succinate, 15 mg. per cc.	2	6.4	2.6	0
	4	5.4	1.9	0
	6	7.0	Dead	—
	8	4.4	3.2	0.13
	10	4.6	2.0	0
	12	3.8	1.8	0
	14	2.6	2.7	Dead
	16	6.2	2.4	0
	Median	5.0	2.4	0
Procaine Penicillin* Control	1	3.2	4.1	0.89
	3	6.0	5.2	0
	5	2.5	2.6	0
	7	4.2	4.0	0
	9	1.6	1.1	0.28
	11	3.6	2.0	0.28
	13	1.6	1.5	0.25
	15	1.4	1.6	0
	Median	2.8	2.3	0.12

*Parencillin—Trademark of The Wm. S. Merrell Co.

The Decapryl concentration in the various preparations has been set, in general, with regard to the difference in frequency of administration of the various penicillin preparations in humans.

The first comparison made in these studies was between the Romansky formula and crystalline penicillin G in oil with 2 per cent aluminum monostearate plus 10 mg. Decapryl Base† per c.c. As seen in Table I, there is little difference between levels or therapeutic duration induced by the two preparations.

Table II contains results of a comparison between crystalline penicillin G aqueous with and without a Decapryl Succinate diluent (5 mg. per c.c.). It can readily be seen that results with Decapryl were as good, or better than those obtained with control.

In the comparison between crystalline procaine penicillin with and without Decapryl Succinate (15 mg. per c.c.) the results in Table III indicate a higher peak for the Decapryl preparation. However, the difference in peaks is not likely to be of therapeutic significance and the number of control animals showing levels at twenty-four hours (four of eight) is not significantly different from the results with Decapryl (one of six). Applying the chi square test we find that such a difference could be due to chance at least once in five cases.

Table IV shows practically no difference between levels obtained with an aqueous fortified procaine penicillin with and without Decapryl Succinate (20 mg. per c.c.).

Procaine penicillin in oil has been evaluated with four levels of Decapryl Base added, 5, 10, 15 and 20 mg. per c.c. The comparison of control and

†Ratio of Decapryl Base to Succinate is 3:4.2.

BLOOD LEVELS—MURRAY ET AL

TABLE IV. COMPARATIVE PENICILLIN SERUM LEVELS
 Decapryl-Procaine Penicillin G Fortified with Potassium Penicillin G and Procaine
 Penicillin G Fortified for Aqueous Injection

Sample	Rabbit	Hours—Units per cc.		
		½	6	24
Procaine Penicillin Fortified* with 20 mg. Decapryl Succinate per c.c.	1	13.0	2.9	0.32
	3	8.2	3.6	Dead
	5	12.0	4.5	0
	7	13.0	3.5	0
	9	11.0	4.0	Dead
	11	12.0	2.7	0.17
	13	12.5	4.2	0
	15	8.8	4.1	0
	Median	12.0	3.8	0
Procaine Penicillin Fortified* Control	2	7.4	2.0	0.41
	4	13.0	2.9	0
	6	12.0	3.8	0
	8	6.3	2.4	0.09
	10	13.0	5.2	0.05
	12	13.0	3.8	0.11
	14	12.0	3.8	0
	16	13.0	4.2	0
	Median	12.5	3.8	0

*Parencillin (Fortified)—Trademark of The Wm. S. Merrell Company.

TABLE V. COMPARATIVE PENICILLIN SERUM LEVELS
 Procaine Penicillin G in Oil—2% AL. Monostearate
 with and without Decapryl

Sample	Rabbit	Hours—Units per cc.		
		24	48	72
Procaine Penicillin* in Oil with 15 Mg. Decapryl Base per c.c.	9	1.10	0.14	0.03
	10	0.55	0	0
	11	0.66	0.26	0.17
	12	0.70	0.14	0
	13	0.73	0.19	0.10
	14	0.89	0.30	0.14
	15	0.95	Dead	—
	16	0.90	0.17	0.03
	Median	0.81	0.17	0.03
Procaine Penicillin* in Oil Control	1	0.46	0.12	0.05
	2	0.46	Dead	—
	3	0.87	0.22	0
	4	0.80	0.16	0.04
	5	1.10	0.26	0.08
	6	0.96	0.13	0
	7	0.14	0.02	0
	8	0.56	0.09	0.03
	Median	0.68	0.13	0.03

*Parencillin (in oil)—Trademark of The William S. Merrell Company.

one Decapryl preparation (15 mg. per c.c.) is presented in Table V. Similar levels were stimulated by the two preparations and the same results were obtained with the other levels of Decapryl except that 20 mg. per c.c. seemed to prolong the therapeutic level, seven of seven animals having therapeutic levels at seventy-two hours.

In checking blood levels of ten patients switched from regular penicillin to Decapryl-Penicillin, Simon⁸ reports four lower, two higher, and four about the same. Therapeutic results were similar for the two preparations.

BLOOD LEVELS—MURRAY ET AL

In five of our studies we found the Decaprym-Penicillin products to be about the same as the penicillin controls. In one study mentioned the level stimulated by the Decaprym preparation was of longer duration than that of the control.

It is evident from the over-all comparisons that Decaprym has little or no effect on the blood levels induced by the various pharmaceutical forms of penicillin.

SUMMARY

1. Penicillin blood level studies were conducted on sera of rabbits injected with various penicillin preparations with and without an antihistaminic (Decaprym).
2. The administration of Decaprym Succinate with various pharmaceutical forms of penicillin produced blood levels of the same order as those obtained when penicillin is given with the customary diluents.
3. Decaprym Succinate did not appear to interfere with absorption of the penicillin.

The authors wish to express their appreciation to Miss K. Ludwig, Mrs. J. Scrugham and Mr. H. Ritter for assistance in the animal studies and to Miss M. Brosch for assistance with the assays.

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FILM AVAILABLE

Twenty additional prints are now available of the film "Allergy: Immunology and Treatment," prepared by the Medical Film Guild, New York, under the supervision of Leo H. Crie, M.D., Department of Immunology and Medicine, University of Pittsburgh. The film, in preparation for eighteen months, is a postgraduate course in allergy, made possible by a grant from Wyeth, Inc., Philadelphia, and Nepera Chemical Co., Yonkers, N. Y. It is available without charge to the profession through the firm of Wyeth, Inc.

Convention Echoes

PREPARATION OF PROGRAM PAPERS AND EXHIBITS

Excerpts from the Presidential Address
by

JONATHAN FORMAN, M.D.

EDITOR'S NOTE: President Forman's Presidential Address, unfortunately, was presented to the Board of Regents only, since time demanded that the length of the business meeting be curtailed, and President Forman obliged by giving up the time for his address. Included in the Presidential Address were such valuable suggestions concerning the submission of papers for future programs and the organization of scientific exhibits that the Board of Regents ruled that excerpts from the address be published in the *ANNALS OF ALLERGY*, and be sent out to all members when papers are solicited for the Seventh Annual Session to be held at the Edgewater Beach Hotel, Chicago, February 11-14, 1951. Let us read these suggestions over several times and show our loyalty to the College by personally endorsing and supporting these suggestions.

WHEN submitting the title of your paper to the program chairman for next year, and each of the following years, accompany it with a press release, some 250 words, of clear, concise, complete expositional writing containing all the facts that the public should know about the field in allergy of which you are writing, and then the logical arrangements of the particular contribution that you are making against this simple background of historical facts. This is imperative for the time element, if for no other reason. The period between the submission of your paper and its acceptance and the completion of the program is altogether too short for the Committee on Public Education to do a re-write job that is satisfactory, especially if they have to write and wire you three or four times because you have not made it clear in ordinary everyday language what your contribution is and how it is related to known facts. Nevertheless, we have no apologies for wide coverage of the recent College sessions in the metropolitan newspapers and the news magazines and weeklies throughout America. If we of the College, however, are to assume our just obligations to see that the people do get the facts about allergy, without distortion, and that they comprehend them, timing is important. You can help immensely if you will follow this suggestion of getting a press release to the Committee of Public Education as early as you possibly can.

And here are two suggestions about your paper that will add interest to our programs. First, *charts and slides that you use must illustrate*, for it is immoral to steal the time of so many people with slides which fail to illustrate because they are over-crowded. No matter how well they illustrate your paper, the rest of us will never know it unless we can read what you have placed upon these charts and slides from our place in the hall.

Presented at the Sixth Annual Meeting of the American College of Allergists, January 15-18, 1950, St. Louis, Missouri.

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So for the sake of all concerned, please keep the wording *simple* and the type *large*. Slides should not take longer than one minute to read.

Now, about the paper itself. Our meetings will be made much more worthwhile in publication if we *shorten the papers and increase their number*. We must follow more and more the worthwhile scientific and learned Societies and train ourselves to give ten-minute papers. There is no point in clinical medicine and certainly no piece of research that cannot be presented within ten minutes if the essayist knows what he is talking about. In fact, eight minutes is adequate at the normal radio reading time of 140 words per minute, equaling approximately 1200 words. This does mean careful writing, meticulous editing and rewriting. It means writing one paper to read and another to publish. This last is very important. In setting up the program this year we ran into a very difficult misunderstanding because one of the discussants had only seen the paper that was to be read when he should have had full data. And so it is also the duty of the essayist to *furnish any formal discussant with a copy of the full paper*.

Incidentally, formal discussants are as a rule a great loss of time to the average person who is in attendance and, therefore, while we recognize the desirability of having as many discussants as possible appear on the program for the promotion of enthusiasm and esprit de corps, we should get more people on the program as essayists and not as discussants.

"We always," as Glenn Frank liked so well to warn us, "are inclined to *overestimate* the amount of information that our listeners have and to *underestimate* their intelligence." I urge, therefore, that you look into the results of the studies that are now going on in the subjects of readability and audience comprehension. Fleich's new book, "The Art of Plain Talk," or the work of Professor Edgar Dale at the Ohio State University will give you techniques for submitting your papers to test formulas which will identify at what level of education your paper is intelligible. The American farmer, for instance, in a recent survey was driven away from the United States Agricultural bulletins by the use of the word "relationships." But the word "relations" he knew and understood. Again in a recent survey made not too long after the death of Mr. Roosevelt, it was found that about 52 per cent of the people queried in a cross section of America had not heard about the United Nations. After some months of operation about a third of the American rural communities had no concept of the Marshall Plan, which certainly was keeping up the price of their products. These people are not dumb, they just have not become interested, and in these days of television, radio, two or three daily newspapers, a couple of weekly magazines and a few quarterly journals of opinion, the average American citizen has built up sales resistance; otherwise, he would be bankrupt. Our attempt to interest him in health education is confronted with a problem of breaking down this immunity. This not only goes for the public in general, but it goes for physicians in other fields of practice. Even here in the sessions of our American College of Allergists, we still have the job of attract-

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ing the interest of our audience. You must be careful not to drive them away from concentrating on your paper by the use of strange words. Each of us allergists has a different perception mass and phrases and words mean different things to each of us. Be we nose and throat specialists, eye specialists, dermatologists, or pediatricians, our particular variety of shorthand language is so specialized that more than 75 per cent of our members cannot understand us if we use our own everyday medical dialect, so let's write briefly and so clearly that our own typist can understand what we are talking about. In fact, if she can't then you had better rewrite your paper, for it will be no good to present to any group of physicians even in your field of allergy. Once your paper has been written, boiled down to 1200 words and rewritten to your complete satisfaction, you are still not ready for the meeting.

If you stop to think about it, I am sure you will agree with me that to make a halting, stumbling, mumbling presentation is a positive insult to your colleagues. You are asking approximately 1,000 of America's leading physicians to spend ten minutes each or a collective period of 10,000 minutes while you present your thoughts, experiences and conclusions. This is something not to be undertaken lightly. You have an ethical responsibility.

So *use a timer as you practice reading your paper*, and you should practice reading it at least a dozen times or more until you are able to do it clearly; fluently and in exactly eight minutes with just the right emphasis on each word so it will convey its real meaning and have just the right value in relation to the other words on the page. You must do this even if it takes twenty-five rehearsals. The more you practice the more effective will be your presentation.

One more thing in this connection. *Remember you are going to have to speak into a microphone.* If you are microphone shy or if you are not experienced in their use, try to do your practicing in front of one. In any event, take your position far enough back of the mike to make yourself heard in all parts of the room without blasting the ears of your listeners.

If we all were to do these things, our meetings would continue to lead in interest and value and our attendance would continue to grow. If we fail to heed these suggestions, our meetings will tend to become dull and as deadly as most medical meetings, and our attendance will not be what it should be.

There is another thing that I would like to say to you who are younger than I—something that I would do myself were I to live my life over again—and that is the fact that *you can do research in your own practice and in your own laboratory.*

We allergists are often condemned by our colleagues, and by some who have set themselves up as arbitrators of our destiny; they say that we are not sufficiently productive. As a matter of fact, these persons who criticize us forget for the most part that we allergists have used up about all the biologicals scientists have been able to offer us for our use in the fields

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of immunology (biological, chemical, physical) and from pathology (anatomical, physiological, and chemical) and related fields. In recent months, however, there has begun to flow a mass of new material from the basic scientists in physics and chemistry that can be and is being applied to immunology and pathology. These men, in turn, will in due course of time be sending to us material which we can apply to our patients, and new light will be shed on the nature of the allergic reaction and its management. Better days are coming!

In the meantime, I would urge that you dig in some place on some phase of investigation, especially you younger men not now connected with medical school faculties, before you take up stamp collecting, painting or specialize in golf—or should I say that golf is a sub-specialty? You should build a small laboratory in or near your home. Keep it out of your office, for it might run your patients out. In your home it can offer you as much fun and recreation as anything you can do, and in a short time you will be able to come to the annual meeting of the American College of Allergists, with a real contribution to its program and, therefore, to Allergy—maybe not an epoch-making, but certainly a definite contribution.

Shorter papers! Snappier papers! Understandable papers! Interesting and attractive papers presented in the best of reading English with charts and slides that do NOT distract, but preferably without either. I would urge that you put your charts, pictures and slides into an educational exhibit and give the men the benefit of a chance to study them.

If you come thus armed each year, your knowledge, your skills, your clinical judgment, and consequently your reputation, will all be so enhanced that you will be repaid a hundredfold for your effort. Just think what we shall make of our Society if as many as 10 per cent of our 1005 members will follow this suggestion. Our meetings would be terrific! Therefore, I would urge you to get busy, whether the other fellow does or does not.

Harold C. Hagen, M.C., representative in Congress, 9th District of Minnesota, presented a petition at the second session of the 81st Congress appearing in the Congressional Record, Vol. 96, No. 38, page 2346, which reads as follows:

"1903. By Mr. Hagen: Resolutions adopted by the American College of Allergists in opposition to any form of compulsory health insurance or any system of political medicine designed for national bureaucratic control; to the Committee on Interstate and Foreign Commerce."

CONVENTION ECHOES

AWARD OF VON PIRQUET MEDAL

President Jonathan Forman, when conferring the Von Pirquet Medal upon Dr. Paul Kallós, presented a brief biological sketch of the recipient:

Dr. Paul Kallós, a Swedish subject, was born in Budapest, Hungary, on December 14, 1902. After having studied and graduated (1920-1926) at the Elizabeth University of Péso, he received his degree of M.D. at the university. From 1924 to 1929, he was research associate and later head of the laboratory of the tuberculosis sanitarium, Baron Friedrich v. Körányi, at Budapest. From 1929 to 1930 he was research associate and clinical assistant at the Pediatric Clinic of the University of Leipzig, Germany. For two years following he was research associate and consulting physician for tuberculosis, internal medicine and diseases in allergy at the Dermatological Clinic of the City of Nurnberg, Germany, where he was in close collaboration with the famous dermatologist, Professor Ernest Nathan. The next year he did research work in Switzerland at the laboratories of the Tomarkin Foundation in Locarno, and the Institute for Research in Tuberculosis at Davos. He was also consulting physician for internal medicine and diseases in allergy at the sanitarium, Kurhaus Victoria, in Locarno, for one year. The next three years he was research associate and consulting physician for diseases of allergy at the Academic Hospital in Uppsala, Sweden, at the invitation of the Nobel-prize winner, Professor Robert Bárány. From 1937 to 1944 he was head of the immunological research laboratory of the Wenner-Gren Institute of Experimental Biology at the University of Stockholm. Since 1945 Doctor Kallós has been specializing in the practice of allergy and doing research in allergy at Helsingborg, Sweden.

Dr. Paul Kallós is Editor of the book series, "Progress in Allergy—Fortschritte der Allergielehre," one of the Editors-in-Chief of the *International Archives of Allergy and Applied Immunology*, and Contributing Editor of the *Quarterly Review of Allergy and Applied Immunology*. He is an Honorary Fellow of the American College of Allergists and of the Argentina Allergy Society; Fellow, Founders Group and Executive Committee of the International Association of Allergists; Secretary, Southern Swedish Allergy Forum; Fellow, Swedish Association of Allergists, Swedish Association of Physicians (Svenska Läkarsällskapet), Medical Society at Lund, Medical Society at Uppsala, Swedish Association of Bacteriologists, Swedish Physiological Society, Scandinavian Association of Physiologists, and the Swedish Association for Internal Medicine.

Research grants have been awarded to Dr. Kallós by: Swedish National Association against Tuberculosis; King Gustaf V's Jubilaeumsfond; Lotten Bohman Foundation of the Caroline Institute, Stockholm, Hedstroms Minnesfond of the University of Uppsala; Swedish Medical Research Council; the Swedish Department for Public Health (Medicinalstyrelsen); and the American College of Allergists.

Dr. Kallós has published eighty-six papers covering his observations during this time.



JONATHAN FORMAN, M.D.



PAUL KALLÓS, M.D.

Recipient of Von Pirquet Medal, 1950

SOME ASPECTS OF ALLERGY

PAUL KALLOS, M.D.

Mr. Chairman and Esteemed Colleagues:

It is with feelings of deep gratitude and devotion that I accept the great honor you have bestowed upon me, the von Pirquet Gold Medal.

In the word devotion is included my loyalty to the work of that great scientist Clemens von Pirquet and to those research workers and clinicians, who have already had this honor conferred upon them: Bela Schick, W. W. Duke, Arthur Coca, Robert Cooke and Milton J. Rosenau. When I think of the great pioneer work which these great workers have done, then I feel that you will permit me to use the word devotion. I am deeply grateful to receive this honor at a time when the American College of Allergists is being led by two such well-known men—not only as scientists but as great international organizers in our field—as Jonathan Forman and Fred W. Wittich.

At the request of Fred W. Wittich I am going to claim your indulgence by giving you my ideas on the allergic diseases. I will begin by saying that I cannot look upon allergic diseases as an isolated and strange group of disorders. My views, on the contrary, are that this group must find a place among all other diseases and that biological laws and features which are valid for all functions in living organisms must be valid also in this case.

I believe that it is too often forgotten that all the symptoms which we generally call "disease" are reactions of a living organism and not direct products of exogenous or endogenous noxious factors which cause them. Independent of the kind of the noxious agents all disease symptoms are expressions of functional or structural disturbances of the diseased organisms. This also means that the same symptoms, for instance fever, pain, disturbances of the circulation and of the volume, chemistry, and cytology of the blood, can be caused by many noxious factors. On the other hand, some noxious agents with special characteristics, such as bacteria or viruses, can in organisms of susceptible species cause reactions, with priority in certain organs. In this way specific diseases arise. Perhaps you will permit me to mention as one example poliomyelitis. If the virus of this disease can invade the central nervous system of an organism of a susceptible species, the metabolism of certain nerve cells will be disturbed and the cells themselves destroyed. This results in the paralysis of a number of muscles. The same virus cannot react with the nerve cells of other non-susceptible species and they therefore do not become paralyzed.

It was Clemens von Pirquet's and Bela Schick's great discovery which showed that the reaction capacity of a susceptible organism will be changed by a first contact with a noxious agent. This change of reactivity can cause a new contact with the same agent to result in reactions which are qualitatively and/or quantitatively different from the reactions shown in connection with the primary contact. The "disease" is the sum of the reactions of the organism to the effect of the noxious agent; therefore the change of the reaction capacity must result in a change of the picture of the disease. Von Pirquet further showed that this change of the capacity to react is a specific one, in other words, concerns only the noxious factor which caused the change. After the first contact the organism produces certain chemical bodies, called antibodies, which have a specific chemical affinity for and can react with the noxious agent which caused them. This reaction between specific antibody and noxious agent can result in a situation in which the functional and structural disturbances, that the noxious agent generally causes in the organism, become weakened or do not appear.

The antibodies affix themselves also to certain tissues. If the cells of these tissues get into contact with the noxious agent the antibody will react on the surface of the

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cells with the agent. This chemical process is a stimulus for the cell, and the cell will answer with its normal function. A muscle cell will contract, a gland cell will produce secretion, a cell of the capillary wall will change its tonus and permeability, etc. The total sum of such reactions can also exceed the physiological limits and appear as a local or general disease. It is quite clear that the symptoms of this disease have no connection with the primary diseasing effect of the noxious agent, but instead they are characteristic for the specifically changed reaction capacity. This is to be understood from von Pirquet's very first work, his letter of April 2, 1903, to the Academy of Sciences at Vienna. He proposes for the changed capacity to react, the name "Allergy" and for noxious factors which can cause such a change, the name "Allergens."

The development of the allergic state can consequently result in weakening or abolishing the special diseasing effect of a noxious agent ("Immunity"), but the "allergic reactions" of antibody-containing cells can at the same time result in local or general disturbances of other kinds, which can reach the state of shock. In this way a close connection exists between immunity and allergy.

So far we have mentioned only noxious agents, that is factors which under certain conditions have a diseasing capacity in the great majority of individuals of a certain species. Von Pirquet has in the serum sickness discovered a disease which is not caused by a noxious factor in this meaning. Blood serum from animals of different species is not harmful or noxious in itself; it is tolerated even in large quantities without reactions which exceed the physiological limits. After a first contact with such a serum the capacity to react becomes changed; the organism becomes allergic; antibodies will be developed and affixed to certain tissues. A second dose of the same kind of serum brings it into contact with these cells and they react, with local or general disease symptoms as the final result. Serum sickness has consequently the same mechanism as the anaphylactic state of experimental animals, discovered by the famous French physiologist Charles Richet and his school, also at the beginning of this century.

In anaphylactic experiments and in the serum sickness the primary contact with the allergen is deliberately produced by a third person. The clear-cut presentation of the American physiologist S. Meltzer (1910), very well known to you all, gave us the conception that the human sickness asthma bronchiale has the same mechanism as the anaphylactic state in experimental animals. We very rightly assume from this the beginning of the clinical science of allergic diseases.

In the case of asthma and certain other diseases, for instance urticaria and eczema (Eli Maschowitz, 1911), the cause of the incapacitating reactions is substances in the environment, which are absolutely inert in the great majority of individuals of the same species. A primary contact with some kind of such allergens (for instance pollens, molds, foods, dust, animal danders, etc.) produces in certain individuals with hereditary disposition an allergic state. This primary contact is established by chance. Antibodies will be produced and affixed to the tissues, and after this every new contact with the specific allergen results in stimulation of antibody-containing cells and consequently in disease. The localization of the antibodies in various tissues or organs, the way in which the allergen reaches the allergic organism, and the quantity of the allergen are the deciding factors as to the kind of resulting symptoms. In these cases the development of antibodies has no useful function; the allergens are certainly no "noxious agents." In 1937 we had proposed the hypothesis that the development of antibodies against innoxious agents is an inherited functional fault. The heredity of disposition to be allergic is proved by A. Coca, A. S. Wiener and others. Not only human beings but also animals can have such a disposition and become allergic, as shown in the important research work of F. W. Wittich.

In this discussion I have not mentioned the fact that living noxious agents, such as bacteria and viruses, have a reproducing capacity and often also produce harmful sub-

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stances (toxins). The invasion of a susceptible organism at a given moment by a number of microorganisms is consequently no endpoint; on the contrary it represents the beginning of a combat, in which the enemy, the invading microbes, sometimes increase in number, invade various organs and disturb their structure and function; the toxins paralyze other functions. The picture of disease so resulting is perhaps dominated by these phenomena. The organism develops antibodies and reacts in many other ways against the harmful effects of the microorganisms. If these reactive processes can prevent the further reproduction of microorganisms and stop the attack or at least localize it to certain limited areas, we get the opportunity of showing the reactions of the organism in a clearer manner.

Allergic diseases *sensu strictiori* are caused by allergens which in themselves are not harmful. As is shown, the production of antibodies against allergens of this kind, antibodies without useful function, leads to reactions of the allergic organism which are out of proportion to the severity of the attack. Thus the allergic state is often called "hypersensitivity," a name which has no real foundation and should be avoided.

The only important fact which concerns us here is that the allergic organism, through its changed capacity to react, can sometimes respond with identical reactions to different kinds of allergens, for instance to living pathogenic microorganisms on the one hand and to innocuous agents on the other. Thus it is not surprising that the same clinical picture can sometimes be produced by living microorganisms as well as by simple allergens, bearing in mind such disorders as "rheumatic" manifestations, nephritis, periarteritis nodosa, etc.

Every stimulation of cells leads not only to direct reactions but also to reactions in other cells as response to the altered functional state and sometimes also to the condition caused by substances, so-called mediators, such as histamine, sympathine, acetylcholine, etc., released from the stimulated cell. In this way a local stimulation will lead to a general reaction of the whole organism. On the one hand the functional disturbances spread, and on the other regulative and reparative processes start.

The first contact with an allergen starts in a susceptible organism a special disturbance in the globuline synthesis. Instead of normal serum gamma-globulines being produced, globulines are produced with altered structure, such as specific antibodies. If the globulin-producing cells have developed some kind of antibodies, then they retain the capacity of so doing even after the elimination of the allergen. In this state every stimulation of these cells can cause a renewed production of antibodies ("anamnestic reaction"). In this way an allergic state can remain for a long period even when contact with the specific allergen is prevented.

Not only have the protein-producing cells such a "memory," but the whole organism has. If an allergic organism has reacted several times to the specific allergen in a special way, for instance by urticaria to eggs, by rhinitis or asthma to pollens, etc., the kind of reaction can be a sort of "conditioned reflex." In this state the reaction, the "allergic disease," can be started not only by the allergen but also by many other influences, and last and certainly not least by psychic ones.

I have tried here to shew only some fragments of the tremendous allergic mosaic and how it appears to me. It is worth noting that our prophylactic and therapeutic measures are directed by the knowledge of the sketched biologic processes. If possible we will prevent the development of allergy in persons with known hereditary disposition; we will in every case try to ascertain the allergens and eliminate them from the environment of the allergic. If an allergic disease is already established, we try to interrupt the chain of reactions, the entirety of which is the disease. Remedies here come to play their part. As W. Hughes (1946) wrote, any remedy which would inhibit the reactivity of the organism without doing harm should cure every "allergic" disease. We are short of such remedies. Perhaps "Cortisone" and ACTH promise something in that direction. All the other remedies only interrupt the chain at some

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special points and give only symptomatic relief. The organism retains the antibodies and also the capacity to react afresh.

The animal experiments of Ch. Richet, Milton J. Rosenau, and A. Coca and the clinical experience of L. Noon, J. Freeman, R. Cooke, W. W. Duke and others showed that repeated injections of the specific allergen can bring about a state in which the allergen will be tolerated by the allergic organism without disturbances. R. Cooke and his school discovered that this treatment, called "hyposensitization," leads to the development of a new kind of antibodies, which do not affix to tissue cells and consequently can react with the allergen without stimulating the cells. The latest results of A. S. Wiener confirm these findings. We are engaged in serological investigations which will enlighten us as to the role of the different kinds of antibodies in the course of the allergic state. I feel that hyposensitization is the most promising therapy at the moment. In my experience it has given about 70 per cent beneficial results.

Much has been done and there is very much left for all of us throughout the world to do. We must work together for this end, and I at this solemn moment, deeply conscious and grateful to you for this great honor, do promise that I will still further devote myself to this great task and look forward to the day when we can meet in person in a peaceful world and refortify ourselves for the work which is still to be done. I thank you all.

THE AMERICAN COLLEGE OF ALLERGISTS

Proceedings of Sixth Annual Meeting

The Sixth Annual Meeting of The American College of Allergists was held at the New Hotel Jefferson, St. Louis, Missouri, January 15-18, 1950. Publication of the program of this meeting is intentionally omitted from the ANNALS, since all members received copies earlier, and because it is necessary to conserve space for an accumulated backlog of manuscripts. Any member desiring an extra copy may have the same upon request.

Owing to unforeseen difficulties and conflicting allergy meetings, it was necessary, in order to secure technical exhibitors, to advance the program somewhat, so that only nine months had elapsed since the Fifth Annual Meeting held at the Palmer House in Chicago. Because of this rather short interval of time the Program Committee experienced some difficulty in securing worthwhile papers, and thus found it impossible to prepare the program bulletins and place them in the mails as long a time in advance of the date of the meeting as it would otherwise have done.

About sixty members who had actually made hotel reservations and planned to attend the St. Louis Meeting found it impossible to be there. Some of these had plane reservations, but could not get off the ground because of poor flying conditions; others who had rail transportation were handicapped by the unusual floods resulting in disorganized train schedules.

Thirty-three technical exhibitors were present and exhibited products related to allergy. Included in this number were the majority of our Sustaining Members. The highlight of the Scientific Exhibits was the three-booth display allotted to ACTH, ACE and Cortisone in Allergy, by Drs. Theron G. Randolph, John P. Rollins, and Michael Zeller.

The two simultaneously conducted scientific programs were a complete success, due very largely to the fact that the more representative allergists in the College were present. Among the highlights of the Session were the Panel on Itching Dermatoses on Tuesday, January 17, at 2 p.m.; the splendid address by our guest speaker, Doctor

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Vera Walker, President of the British Association of Allergists, of London, England; and the presentation of the Von Pirquet Medal, *in absentia*, to Dr. Paul Kallós of Sweden. All in all the program was an excellent one, largely owing to the untiring efforts of the Program Committee, of which Dr. Sim Hulsey was chairman. Much credit is also due to Dr. Jonathan Forman, who personally handled all the advance publicity for the meeting and whose inspired leadership alone would have assured its success.

A most successful cocktail party in the Gold Room on Monday evening served as a medium for promoting good fellowship. Since the majority of the members had made plans for, and had expressed a preference for, private dinners and entertainment, it was decided to dispense with the customary annual banquet this year and in succeeding years. A spirit of great cordiality and enthusiasm was everywhere in evidence throughout the entire meeting.

Next Annual Meeting

By unanimous action it was decided to hold the next annual meeting of the College at the Edgewater Beach Hotel in Chicago, February 11-14, 1951. It will be preceded (February 9-11) by a three-day intensive Graduate Instructional Course in Allergy. Dr. Albert V. Stoesser, Chairman of the Program Committee, and his associates, President John Mitchell and Secretary-Treasurer Fred Wittich, have already arranged the schedule for the Instructional Course, which is to be made available to all registrants attending the College Session; and the committee promises that it will feature many innovations.

Registration will begin on Sunday, February 11, at 2 p.m., and will not in any way interfere with attendance at the Instructional Course. There will be no Technical or Scientific Exhibits on Sunday. These will be featured on Monday, Tuesday, and Wednesday, February 12, 13, and 14. A Scientific Program will also be held on these same days.

Brief Résumé of Business Transacted

The Secretary-Treasurer reported a total membership of 1,005, including all classes. Two members were advanced to Active Fellowship, making a total of six so advanced during the past year. The list includes Thomas W. Collier, M.D., Captain Ross Imburgio, M.D., John F. Kelly, M.D., William H. Lipman, M.D., Ronald V. Silknetter, M.D., and A. Harvey Simmons, M.D. Hereafter the Secretary-Treasurer will make a survey of members preceding the annual meeting to determine which warrant promotion to Active Fellowship, and the list so submitted by him will then be acted upon.

During 1949 the College sustained, through death, the loss of the following members: W. Byron Black, M.D., and Arthur Kalisch, M.D. Obituaries appeared in the *ANNALS OF ALLERGY*, and condolences were sent to the families.

At the general business meeting held on Tuesday, January 17, the following officers were elected to serve during the ensuing year and until their successors are duly elected and qualified:

Officers

President-Elect—Harold A. Abramson, M.D.
First Vice-President—Theron G. Randolph, M.D.
Second Vice-President—Susan C. Dees, M.D.
Secretary-Treasurer—Fred W. Wittich, M.D.
Assistant Secretary-Treasurer—Albert V. Stoesser, M.D.

Board of Regents

<i>One-Year Term</i>	<i>Two-Year Term</i>	<i>Three-Year Term</i>
Harold A. Abramson, M.D.	Hugh Kuhn, M.D.	L. O. Dutton, M.D.
Robert F. Hughes, M.D.	John D. Gillaspie, M.D.	Norman W. Clein, M.D.
Boen Swinny, M.D.	Herbert Rinkel, M.D.	Stephan Epstein, M.D.

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Doctor Wittich presented a complete financial report covering the *ANNALS OF ALLERGY* for the year ending November 30, 1949, reflecting a total profit of \$7,082.53 as compared to \$6,868.38 for the preceding year. Fifty per cent of this amount goes to the College.

Mr. Eloi Bauers, Counsel for the College, discussed the legal aspects of, and the questions involved in, the renewal of the contract with the Bruce Publishing Company for publication of the *ANNALS*, and upon his recommendation it was decided to continue the same in force for a period of three years from last November, 1949.

The Finance Committee report, given by Dr. Boen Swinny, showed an operating profit of \$4,631.29 for the calendar year 1949, as compared with an operating loss of \$1,136.54 for the preceding calendar year. Upon recommendation of this committee, it was decided that hereafter the publication of panel discussions, such as "Psychodynamics and the Allergic Patient," will not be supported by the College because of the extra work it places on the staff and because the work and time involved are out of all proportion to the profits realized therefrom, and that in the future the College will confine itself, so far as publications are concerned, solely to the *ANNALS OF ALLERGY*. All authors will be requested to furnish the College with translations of manuscripts. Letters addressed to the College will, of course, continue to be translated at College expense.

The committee recorded its opposition to the use, in future years, of funds obtained from initiation fees for the purpose of helping to defray current expenses. It feels that the ultimate objective of the College should be the payment of all operating expenses solely from the income received from membership dues collected, plus such revenue and profit as may result from instructional courses, which, it was decided, will hereafter be held in connection with, and immediately preceding, annual meetings. These courses are to be geared to the student interested in allergy, and instructors will be expected to pay their own expenses, since they will be attending the annual meeting of the College at the same time.

The committee decided not to set up a proposed budget for the current year's expenses, but rather to recommend that expenditures, in 1950, in each category enumerated in the current audit report be limited, as far as possible, to the amount actually spent for such items during 1949.

By appropriate and unanimous action the annual dues for both Active and Associate Fellows were increased by the sum of \$5.00.

Action was taken to set up a Pediatric Committee with Dr. Bret Ratner as chairman, for the purpose of stimulating interest in pediatric allergy, with authorization to the committee to set up a morning program on pediatrics at the Edgewater Beach Session in February, 1951.

The College placed itself on record as opposing any form of compulsory health insurance or any system designed for national bureaucratic or political control of medicine, and copies of this resolution have gone forth, not only to the President of the United States, but also to many members of Congress. These latter were respectfully asked to use every influence at their command to prevent the enactment of such legislation.

Doctor Wittich reported on a survey of various medical societies which he was instructed to make for the purpose of developing a section on allergy under the auspices of the College. He reported to the Board that six state societies, including New Jersey and Louisiana, are now offering well-rounded programs in allergy. The New Jersey section meets every other year. Florida and Connecticut have state allergy societies which meet on the day immediately preceding the meeting of their state medical societies. Minnesota will establish a section in 1950 under the auspices of the College. Eighteen societies replied that they were referring the resolution to the proper committee. Five of those replying stated that they were not interested be-

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cause of an insufficient number of doctors in their respective areas, and because they did not have separate sections of any kind in the meetings of their respective state medical societies.

Authority was given Dr. Harold Abramson to arrange for a course to be known as "Psychotherapy for Allergists," to be given under the auspices of the College by Dr. Sandor Rado, at Columbia University in New York City, November 6-10, 1950.

The Committee on Rheumatism and Arthritis was authorized to continue its research work as funds are made available for the purpose, all such appropriations to be kept under the supervision of the Secretary-Treasurer and to be credited to "research funds."

It was also decided that as the Committee on New and Unused Therapeutics makes further detailed studies of new drugs, such studies will from time to time be published in the ANNALS OF ALLERGY. A booklet will also be prepared on basic dust-elimination precautions, to be printed and put on sale, or distributed through members of the College and others.

The Pollen Committee stressed the need for more standardization on the collecting, handling, labeling, and storing of dry pollen.

A resolution was adopted amending the By-Laws so as to provide for the creation of the office of Assistant Secretary-Treasurer, and such other additional offices as the Board from time to time may designate and fix. Dr. Albert V. Stoesser was thereafter elected Assistant Secretary-Treasurer.

The Nominating Committee, after extensive discussion and consideration, presented the following official slate of officers to be voted upon in 1951.

Officers

President-Elect—J. Warrick Thomas, M.D.

First Vice-President—G. Estrada de la Riva, M.D.

Second Vice-President—L. Dell Henry, M.D.

Secretary-Treasurer—Fred W. Wittich, M.D.

Assistant Secretary-Treasurer—Albert V. Stoesser, M.D.

Board of Regents for a Three-Year Term

Bret Ratner, M.D.

Hyman Miller, M.D.

Walker L. Rucks, M.D.

It was decided, in view of the changes made in the several By-Laws at this meeting, as well as numerous other changes and amendments made during the past several years, that the corrected By-Laws, additions and amendments to date be arranged and published in booklet form, and that after the printing proofs have been prepared they be sent to all members of the Board and to the Editor of the ANNALS for any final corrections before publication, after which they are to be returned to Mr. Bauers for final study and then on to the Secretary-Treasurer who will arrange for the printing.

Dr. M. Murray Peshkin reported on the progress made toward certification in allergy by the American Society of Certified Allergists, and was given a vote of continued confidence and appreciation for his untiring efforts.

Progress in Allergy

ANTIHISTAMINIC AGENTS

A Review

ETHAN ALLAN BROWN, M.D., F.A.C.A.

WILFRED KRABEK, M.S.

Boston, Massachusetts

HISTORICAL SURVEY

The work of Dale and Laidlaw in 1910,¹ of Dale in 1920² and 1929³ and others has provided evidence in favor of the now quite generally accepted theory that anaphylaxis is due to the combination of antigen with antibody within the cells of the body, which are thereby damaged. The resulting symptoms may be due, in part, to this damage and in part to the release of histamine, histamine-like substances and other substances of which heparin is probably one.

In 1910⁴ and 1911,⁵ Barger and Dale showed that histamine was present in naturally occurring materials, i.e., in ergot and intestinal mucosa. In 1927, Best, Dale, Dudley and Thorpe⁶ suggested that histamine was liberated from the tissues of the animal body by cell stimulation, due to the inter-action of antigen and antibody. In 1931, Watanabe^{7,8} demonstrated that the lungs of guinea pigs, and the livers of dogs were considerably reduced in their histamine content after anaphylactic shock.

Dragstedt and Gebauer-Fuelnegg⁹ in 1932 reported the presence of a histamine-like substance in the blood and lymph of a dog during anaphylactic shock. In 1936, Dragstedt and Mead¹⁰ showed that the amounts of histamine in the inferior vena cava blood above the diaphragm in the anaphylactic dog were very similar to those required to produce the same changes by intravenous injection.

In 1927, Lewis¹¹ described the triple response of the skin to histamine and pointed out its resemblance to allergic urticaria and to the effects of various other forms of injury.

Lewis and Grant¹² in 1926 compared the reaction of histamine and fish extract in a fish-sensitive patient and found that when histamine and the fish extract were punctured simultaneously into the patient's skin, the resulting reactions were identical.

Hare¹³ examined a pollen-sensitive and two horse-sensitive patients and found that pollen extracts and horse extracts also produced the three-fold skin reaction of Lewis.

In a child suffering from cold allergy Bray¹⁴ observed that the triple response of Lewis resulted when the patient immersed his hands in water at 45 degrees F, indicating that while the physical allergies were presumably not immunological in nature they might be mediated, at least in part, by histamine or a histamine-like factor.

Horton, Brown and Roth in 1926¹⁵ and Rose in 1941¹⁶ found a slight increase in blood-histamine after skin stimulation in cases of dermographism. In this respect it should be noted that while various local effects may be due to the release of histamine, the quantities released may be insufficient to be detectable in the blood and the amounts that reach the blood stream are normally quickly removed. Also, there is a wide range of sensitivity to histamine in different individuals, both allergic or non-allergic.

To summarize, histamine (or histamine-like substances) appears to be present in small amounts in practically all tissues, either as a progenitor, in a combined form, or possibly free in extremely small amounts. It possibly acts as a mediator or

Dr. Brown is physician-in-chief, Allergy Clinic, Boston Dispensary, Boston, Mass., and director, Asthma Research Foundation Inc., Boston, Mass.

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regulator for physiological processes and under certain circumstances, it appears to result in certain pathological states.

Among the considerable number of reviews on histamine, its derivatives and its pharmacological action, are those of Feldberg and Schilf in 1930,¹⁷ Guggenheim in 1940,¹⁸ Dragstedt in 1941,¹⁹ Feldberg in 1941,²⁰ Rocha e Silva in 1942,²¹ Code in 1944,²² Selle in 1946²³ and Rose in 1947.²⁴

In view of the increasing evidence of the important role that histamine appears to play an allergic phenomena, it is natural that any evidence of antihistaminic action of drugs would immediately be utilized. Many drugs, such as epinephrine, atropine, papaverine and other sympathomimetic substances, antagonize the action of histamine through their antagonistic effect on the tissues involved. They are, however, relatively non-specific for histamine-mediated conditions. They frequently affect only one or a few phases of the allergic reaction.

The usefulness of histaminase as an antihistamine is controversial. Feinberg in 1946²⁵ was of the opinion that it lacked any specific effect in allergic conditions.

It is not the purpose of this paper to discuss the relatively non-specific drugs, but to review briefly what are commonly called the "antihistaminic" drugs. Histamine antagonists of antihistamine agents have been ably defined by Loew²⁶ as "drugs which are capable of diminishing or preventing several of the pharmacological effects of histamine and which do so by a mechanism other than the production of pharmacologic responses diametrically opposed to those produced by histamine. True antihistaminic agents are able to antagonize histamine without eliciting pharmacologic responses, or if responses are elicited, they do not appear to be of the type or degree which suggest an important causal relationship to the histamine antagonism." In this paper those drugs will be considered which, from the available evidence, appear to block the action of histamine with some degree of specificity; which are relatively non-toxic to humans and are, for the most part, available commercially either as "new drugs" or as drugs which have undergone relatively extensive clinical trial. This eliminates agents such as atropine, epinephrine and the like, the effectiveness of which in antagonizing other spasmogenic agents of different physiologic types is frequently greater than their effect on histamine-induced conditions.

A number of excellent reviews have been published on various aspects of the antihistamine drugs. These reviews include those of Loew²⁶ on their pharmacology, Hutter^{27,28} on their chemistry and pharmacology, Hunter and Dunlop²⁹ on their pharmacological aspects, Feinberg²⁵ and Haley³⁰ on their clinical uses.

The rationale of the use of the antihistaminic agents rests on two theories: (1) that symptoms of anaphylactic shock are due, in part at least, to a liberation of histamine, and (2) that allergic disease in man is the counterpart of anaphylaxis.

A more or less quantitative correlation appears to exist between a given amount of histamine and the more effective of the antihistaminic drugs. It is upon this relation that the use of the term antihistaminic is justified. Hutter considers that in order to be considered specifically as an antihistaminic, activity at least of the order of 1-10 $\mu\text{g./ml.}$ of bath liquids should counteract the contracting effect of 1 $\mu\text{g./ml.}$ of histamine as tested on the isolated guinea pig small intestine. Other tests as to protection against histamine-produced symptoms must also be satisfied.

In animal tests and in clinical experience, it has been found that the antihistaminics do not counteract all of the pharmacological properties of histamine. This may be due to a number of reasons. The antihistamine drugs may act through adsorption or other combination with histamine receptors, thus directly blocking off the histamine. This would explain the action, in some cases, of the antihistaminic moderating histamine activity to a greater extent when introduced into the tissues before the histamine, than when applied simultaneously or afterward. Under other circumstances, the reverse may be true. Histamine evidently has a number of receptors, presumably many of them different from each other. Therefore, if the anti-

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histaminic drug acts by virtue of the similarity of its structure to histamine, as there is some evidence that it does, a consideration of the stereochemical relationships would lead to a possible explanation as to why some antihistamine compounds vary in both type and degree of activity. Spatial relationships may permit ready combination with some of the histamine receptors and little or none with others. The relatively high (240 and up) molecular weight of the more effective histamine antagonists would seem to bear this out.

The size and shape of the groups at the ends of the key grouping quite possibly determine the degree of blocking of the histamine as well as the ability of the antihistaminic molecule to replace the histamine already in contact with its receptors.

Another factor which may be considered is the so-called intrinsic and extrinsic histamine. If the histamine is released, whatever the mechanism, in close proximity to the histamine receptors there is certain to be less opportunity for a foreign substance (the antihistaminic agent) to counteract it than if the histamine is released in one place and has to travel by the humoral system to the location of its receptors. In this case, the permeability of the cell membrane to the antihistaminic substance may well play a part, particularly since some of the antihistaminic drugs are said to be surface active. Factors that may affect the application of the antihistamine drugs include solubility, degree of hydrolysis, which in turn may affect the solubility or absorption, and the rate of absorption of the compound. Lack of activity on the part of the antihistaminic obviously might be due to a number of factors in addition to those just stated. Among these are the possibility or even the probability that histamine has a number of quite widely different types of receptors resulting in widely different symptoms. Some of these receptors may not correspond to a sufficient extent with the spatial relationship of a given antihistaminic, resulting in a lack of favorable activity on the part of the latter. It may also be possible that some of the symptoms ascribed to histamine are either not due to histamine or are due to the combined action of histamine with another pharmacological agent, as for example, acetylcholine.

The antihistaminic agents are frequently classified as derivatives of ethanolamine (Benadryl) or ethylenediamine (Antergan). A somewhat more basic unit so far as functional structure is concerned would seem to be that of the ethylamine skeleton. Essentially all of the compounds which have to a considerable degree at least, a relatively specific antihistaminic action, contain this group. It may be in the form of a "straight chain" compound such as Antergan or as part of a ring compound such as Antistine. If this group is taken as basic, then such widely different (structurally) compounds as Thephorin, Antistine, Perazil, Trimeton and Phenergan, as well as most, if not all, of the other antihistamines, that have shown sufficient promise to reach the commercial stage, show a common factor. This is not true if ethanolamine or ethylenediamine are taken as basic units, even though they may be the actual starting point for the synthesis of the compounds. This ethylamine skeleton also corresponds to the side chain of the histamine molecule and to part of the imidazole chain.

A correlation of the extensive published literature on the antihistaminic compounds arranged according to groups attached to the basic unit, with the apparent degree of antihistaminic activity, the effect on various allergic symptoms and side effects should prove interesting and might well lead to new lines of investigation. Work in this direction has been done to a varying degree in a number of papers,^{20,21,22,23,24,25,26} particularly in regard to direct antihistaminic activity.

Apparently the terminal nitrogen should be a tertiary nitrogen (Kohler²¹) to attain significant antihistamine activity although it may be part of a heterocycle as in Linadryl or Pyrrolazote. Methyl groups on a terminal nitrogen appear to result in a less toxic product than ethyl groups. The same appears to be true when the

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methyl groups are part of a ring structure such as Perazil and Linadryl. Other energy factors probably play a part in these cases.

Ether linkages on the carbon of the basic ethylamine skeleton appear in general to lead to more toxic products (929 F and Benadryl), although the groups attached to the ether oxygen have a definite modifying action. For example, Benadryl is much less toxic as well as less active than 929 F and Decapryl appears to be less toxic than Benadryl. In Benadryl, the thymol group of 929 F has been replaced by the benzhydryl group. In Decapryl, one of the phenyl groups of Benadryl has been replaced by an alpha pyridyl. Use of beta or gamma pyridyl instead of alpha pyridyl, at least in the Pyribenzamine series leads to a decrease in activity.³⁵ Replacement of a benzyl group by a phenyl³⁶ or a halogenated phenyl group³⁷ leaves essentially the same activity.

Among some of the newer compounds of a different structure are the thiophene derivatives such as Pyrrolazote, Phenergan, 3356 RP, and the pyridindene (or indenopyridine) derivatives as for example, Thephorin. In the case of Thephorin the basic unit is included entirely in the pyridine ring.

The antihistaminic effects of various compounds are evaluated in a number of ways. One of the difficulties in evaluating results from different laboratories is the variation in techniques, frequently omitting the necessary data for, at least, an indirect comparison. Briefly, the following methods are in use: (1) inhibition of the histamine-induced contraction of isolated guinea pig intestinal strip by prior application of the antihistaminic; (2) relaxation of the intestinal strip by application of the antihistamine after the contraction has taken place; (3) counteracting the contraction of a tracheal chain made from the trachea of a guinea pig; (4) prevention of histamine poisoning in the guinea pig due to subjection to aerosolized histamine; (5) prevention or alleviation of histamine intoxication caused by one of several methods of application, for example intraperitoneally, depending upon the type of reaction it is desired to observe. In the clinical evaluation of the antihistaminic agents the results must be considered with care. Many of the tests do not have adequate controls. In some cases the apparent alleviation with placebos alone may run as high as 33 per cent.

Some of the antihistaminic agents show unexpected activities. Brewster and Dick³⁸ found that Benadryl had a significant bacteriostatic activity. They found that the blood reached inhibitory levels after treatment for twenty-four hours at the rate of 50 mg. every four hours. In connection with this must be considered the observation of Halpern and Reber.³⁹ They found that 80 per cent of the animals infected by subcutaneous injection of *Salmonella typhimurium* or *staphylococcus* and then treated with an unspecified amount of Phenergan, developed septicemia and died. Controls similarly infected, but not treated with the drug, survived. It is assumed that the drug, in preventing the edema, destroyed a natural barrier to the diffusion of the infection in the body.

Pellerat (cited by Huttner²⁸) has given a possible explanation of so-called histaminoid accidents which may be associated with the use of antihistamines. He suggests that histamine released by the antihistaminic agent from receptors which have a preferential affinity for the antihistaminic agent may be set free and travel by the humoral system to another group of receptors which are inadequately protected, either by an insufficient amount of antihistamine or by a lesser affinity for it than for histamine, thus setting up a remote reaction. Since the more powerful the antihistaminic agent the more it is taken up by the tissue, Pellerat suggested that more histaminoid accidents might be expected with the availability of powerful antihistaminic agents.

The antihistaminic agents were found by Winter⁴⁰ to have a potentiating effect on the sedative action of barbiturates, hence the ingestion of barbiturates with antihistamines must be used with caution.

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Dreyer⁴¹ has summarized some of the activities of the antihistamine drugs essentially as follows: Some "possess local anesthetic properties, they have atropine-like, antispasmodic, quinidine-like, demerol-like and musculotropic actions, . . . some antihistamines sensitize to epinephrine while others desensitize. The antihistamines have dual actions on some tissues as shown by their effects on striated muscle. In small concentrations, there is increased contraction due to indirect (nerve) stimulation. In high concentrations, indirect stimulation is suppressed, presumably because of block at the myoneural junction but contraction is not inhibited upon direct stimulation of the muscle. Similarly, the antihistamines depress impulse transmission at autonomic ganglia. In the autonomic system, cholinergic responses are partially or completely depressed, depending upon the drug used, whereas adrenergic responses are usually undiminished and may even be potentiated by some drugs." Some drugs "in small doses depress intestinal motility but in large doses they stimulate. Other drugs stimulate motility in small doses but depress in large doses."

CLINICAL REVIEW

In any review of the antihistaminic drugs, one very important consideration must constantly be kept in mind. There are, at present, no means by which the effects of such agents can be measured with any accuracy in man. The papers, which deal with clinical evaluation, concern data which cannot be reproduced excepting within very wide limits. The environment, as regards inhalants, pollens and moulds, changes continuously. In addition to symptomatic treatment, the patients frequently receive both injection and psychotherapy. No two environments or seasons, no two patient populations are identical. The method of clinical evaluation varies with each physician who has his own interpretation of the patient's necessarily subjective report. One patient may complain bitterly because he has thirty minutes of symptoms each morning, while another considers himself blessed because his symptoms are limited to only half an hour.

The toxic effects in animals vary greatly from those seen in man and there has so far been no predictable correlation between the effects in the experimental animal and in human beings. In any case, the effects are multiple and the good results seen may as often be due, as for instance, to sedation in Benadryl, as to stimulation as seen in Neohetramine, as well as to other effects not directly related to those antihistaminic in nature. Without exception, all of the histaminalytic drugs cause side reactions. No regularity of pattern response is known, although millions of doses have been administered. A drug, which causes severe side reactions in one patient, may be taken by another with no ill effects. Another drug, of supposedly lower toxicity, may cause unbelievably severe untoward reactions in a susceptible individual. In some patients, such reactions may be caused by two drugs of dissimilar origin, while in others, another drug of similar but not identical chemical structure can be taken with impunity.

The antihistaminic agents are inconsistent in their action, in that a drug may be effective at one time for a patient and not for a second administration, although the patient's condition may appear to be the same. Ineffectiveness is also capricious. In occasional patients, prolonged administration of a drug which causes side reactions may lessen them, while in others, each successive dose brings on more severe side reactions until the patient is completely intolerant of even the smallest dose. There is no predictable method of deciding whether the patient will benefit from any one drug, although it is usually the rule to administer the drug which is either known to have the smallest percentage of side reactions, or the greatest degree of efficacy.

All of the following reactions have been listed in the literature and the greater number of these are undoubtedly authentic. Others, limited to one drug, will be described in the course of the review. By far, neuropsychiatric reactions are most common. They include drowsiness, dizziness, faintness and fainting attacks, mental

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confusion, incoordination, disorientation, stupor, narcolepsy, coma, giddiness, general hallucinations, apprehension, nervousness, weakness, fatigue, light-headedness, headache, amnesia, lassitude, checked speech, slurred speech, somnambulism, a sense of exhaustion, irritability, athetoid movements, spastic jactations, acute melancholia, suicidal tendencies, bilateral tinnitus, peripheral neuritis, insomnia, tremor, a sense of relaxation, mental lethargy, "walking on air," acute hysteria, jerky and rapid speech, and "an all gone feeling in the pit of the stomach," as well as generalized numbness.

In the ophthalmic system, the patient may complain of photophobia, dimming of vision, dilated pupils, rapid nystagmus, difficulty in accommodation, blurring of vision, and visual hallucinations. Other side reactions include muscular aching and twitching, low back pain and genito-urinary symptoms as impotence, incontinence, bladder discomfort and frequency.

In the respiratory, alimentary and cardiovascular systems, the patient may complain of a dry nose, dry oral cavity, a bad taste, chloroform-like taste, olfactory hallucinations, epigastric distress, nausea, vomiting, indigestion, pyrosis, sore tongue, abdominal cramps, constipation or diarrhea. In some patients, indigestion has caused bronchial asthma and, in others, respiratory arrest requiring artificial respiration. There may be complaints of excessive perspiration, cold extremities, digital vasospasm, hot flashes, shock-like reactions and chills, as well as orthostatic hypotension, true hypotension, palpitations, elevated pulse rate, a tendency to bleeding and facial edema.

In the skin, an aggravation of the original symptoms may be seen, as well as urticaria and generalized pruritus, eczematoid dermatitis, pityriasis-rosacea-like reactions and erythematopapular eruptions.

Since patients who take the antihistaminic drugs may be the subject of study for other conditions, it is important to note such effects which the drugs do not appear to possess. Of these, Benadryl has been the best studied, and it has been demonstrated to be without effect on the basal metabolic rate or the body weight, although other antihistaminic drugs lower the basal metabolism. Taken orally, it does not affect the eye, in which topically applied 0.5 per cent solutions cause moderate dilatation, while stronger solutions cause accommodation interference. Doses up to 300 mg. effect no change in the pulse rate or the electrocardiogram, although systolic blood pressure may be lowered. Occasionally, severe hypertension may occur. The urine is unchanged for its constituents, volume, the urea nitrogen or the non-protein nitrogen. Dilution and concentration tests remain within normal limits. Circulation time is unchanged. Blood chemistry and blood constituents remain normal, although granulocytopenia may appear. Benadryl is reported as increasing gastric acidity in the young and decreasing it in the elderly, although following stimulation with histamine. In doses up to 400 mg. Benadryl has no effect upon the glucose-tolerance curve, although doses of 30 mg. intravenously may increase the glucose-tolerance, while decreasing the body temperature approximately 1 degree F.

The wheal following intradermal histamine is decreased, but the wheal resulting from the injection of trypsin, horse serum or staphylococcal toxin in sensitized animals is not affected. The development of the Arthus-type of reaction following horse serum injection is not prevented by either Benadryl or Pyribenzamine.

ANTERGAN

In an epoch-making communication which appeared in December of 1942, Halpern⁴² described two Rhone-Poulenc compounds 2325 and 2339 (Antergan) as representative of a new class of substitute polymethylene diamines, which were extremely active against the asthma induced by histamine. The author stated that since the new compounds were only weak spasmolytic agents, their antagonism to histamine was due to specific inhibition of the stimulating action of histamine on the bronchial muscles. The minimum protective dose of 2339 RP was 1 mg./kg. in guinea pigs. The LD₅₀ was 175 mg./kg. and 5 mg. of 2339 RP per kg. completely protected the

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animals against 40 lethal doses of histamine. In the dog, the compound prevented the appearance of anaphylactic shock as marked by hypotension and hemoconcentration. Oral administration required ten times the parenteral dose to show prophylactic action. It was considered that the ineffectiveness by the oral route might be due to delayed gastrointestinal absorption, since the protective action was not evident until forty to fifty minutes after ingestion and histamine antagonism was still evident six to eight hours afterwards.

In an attempt to discover the influence of synthetic antihistamines on antibodies seen in anaphylactic shock, Halpern⁴³ later sensitized rabbits with intravenous injections of suspended lamb erythrocytes diluted 1:10 and then gave them anaphylactic doses of 2, 3 or 5 c.c. of the same antigen. Three of the seven rabbits were protected by 40 mg./kg. of Antergan, but all seven died immediately or within two hours. The antibodies measured in blood samples collected five minutes after the injection of the antigen did not fall appreciably. Any slight decline noticed was attributable to previous sampling. Halpern concluded that this method was unsatisfactory for studying the effects of antihistaminics on antibody formation because the sensitization itself produced such a high proportion of hemolysins that lethal injections of the antigen could not appreciably lower the proportion of antibodies in the rabbit blood. These conclusions are important inasmuch as no test for the measurement of the effect of antihistaminic agents on immunological phenomena has as yet been devised. On the other hand, in an experiment with Pasteur Vallery-Radot, Halpern⁴⁴ showed that when rabbits were sensitized with horse serum and then twenty to thirty days later given intramuscular Antergan in doses of 40 mg./kg., followed in fifteen to thirty-five minutes by intravenous administration of horse serum in 3 c.c. doses, no anaphylactic reactions could be observed, although another serum injection within eight to thirty-two hours after the first caused hypotension in eight animals, one of whom died. The surviving animals were all thrown into anaphylactic shock when tested five days later, whereas only one such reaction occurred in seven control animals. Antergan is, therefore, considered as having eliminated the period of anaphylactic tachyphylaxis. The authors state that the P-K reaction in man appears only in three to four hours, rather than one hour after an Antergan injection if a histamine antagonist is ingested two to three hours before the injection.

In an attempt to discover the properties of the new drug, a number of experimental studies were done, including among others, the effect of the ingestion of Antergan upon the erythematous area, provoked by intradermal histamine. Warembourg and his colleagues⁴⁵ discovered that doses of 0.6 gm. decreased such an area when taken for three days before the injection was given, larger doses causing a notable diminution but no inhibition of such intradermal histamine injections.

In 1945, in the Foreign Letter Section of the J.A.M.A.,⁴⁶ Antergan was described as a histamine antagonist, which caused the pruritus due to serum sickness to disappear in half an hour. It was effective, as well, in urticaria, acute eczema, medical dermatoses, and in asthma. It was not uniformly effective in migraine, and had little beneficial effect in arthralgia or shock. The side effects were described as nausea, vertigo, anorexia, "gastric burns." It was said to be tolerated better by children than by adults. The same letter described Neo-Antergan as being three times as potent as Antergan, as well as less toxic. It was stated that well-tolerated doses cause 90 per cent improvement in asthmatic patients. The histamine production was not inhibited but an ability to react to histamine was lost by the tissues during treatment with the drug.

The treatment of bronchial asthma with Antergan by Strengers and his co-workers⁴⁷ had as its object the determination of histamine level in the blood of asthmatic patients; the relation, if any, between the histamine level and the severity of the asthma; the therapeutic effect of Antergan and whether the success of Antergan treatment was related to an initially high histamine level in the blood. For this pur-

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pose, the authors treated forty-six asthmatic patients, administering Antergan orally and by injection. The histamine levels were determined by Code's method, the normal being taken as between 3 and 13 mg./100 ml. No correlation between the histamine level and the duration of severity of the asthmatic complaints at the time the blood samples were taken was found. Eight cases of twenty-three are reported as giving excellent results; six fairly good and five no improvement. In four patients, the first course of treatment gave good results, but the patients did not respond to a second course given several months later, following a relapse. There was an initial elevation of the histamine level in ten of the twenty-three patients and all of these ten improved. Of twelve patients with normal histamine levels, six improved and six did not respond. The authors concluded that there were two groups of asthmatic patients; those with normal and those with elevated blood histamine levels. They suggested that the low levels in some patients might be due to the intervention of some defense mechanism, although there was no direct evidence for this conclusion, with favorable results seen in some patients as compared to the complete lack of response in others, which suggested the possibility of a "histamine-asthma" group. The response of four patients to the first course and not to the second might demonstrate that the drug lost its effectiveness upon continued administration. The authors felt, however, that Antergan should be given to asthmatic patients who had a high blood histamine level.

Further clinical studies with Antergan by Serafini⁴⁸ showed that the drug did not suppress gastric hypersecretion as caused by histamine, although it caused a constant increase in potassium and slight variations, generally decreases, in blood calcium. Serafini reported Antergan as giving beneficial results in eighty-four of 140 cases of allergic disorders, the best results being obtained in acute and chronic urticaria, pruritus and hay fever. Secondary reactions were observed in forty-five patients. In a later study, Serafini⁴⁹ reported the effect of Antergan and also of Neo-Antergan, Antistine and Phenergan as well as Benadryl upon histamine and allergic wheals in normal and allergic individuals. Intravenous administration caused anti-histaminic effects which occurred much sooner than after oral administration, which was not constant in its time, perhaps because of the different absorption rates of each drug. Skin reactivity, although inhibited, returned to its previous state two days after the drug was discontinued. Undesirable, but not serious, side reactions occurred in 25 per cent of the patients treated. The 140 patients previously described as receiving Antergan could be divided into three groups, of whom eighty-four (60 per cent) were completely relieved; thirty-six (25.6 per cent) were partially relieved; and twenty (14.4 per cent) showed no improvement.

In common with the other antihistaminic agents to be described below, Antergan has been used in non-allergic spasmotic conditions. Ameline⁵⁰ used it and Neo-Antergan in the treatment of dysmenorrhea. Beginning when pain first appeared, the patients took Antergan in doses of 0.05 gm. every hour until they obtained relief. They refrained from other medication. The total dose never exceeded 0.5 gm. Some patients required two courses of treatment the remission varying from eight to fourteen months after a single course of antihistaminic therapy.

Antergan has also been used in the treatment of Parkinson's disease by Gerest and Nicollet.⁵¹ Three patients were improved markedly and one temporarily. The treatment failed completely in three patients and was not much more successful in three others. The akinesia was most favorably affected.

The effect of antihistaminic agents on patients with peptic ulcer was studied at an early date. Doscherholmen⁵² reported on Antergan (Lergitin in the original paper) in spontaneous and histamine-stimulated gastric secretion as seen in nine patients, five of whom have gastric ulcers, three dyspepsia and one hypertension. A single dose of 0.2 gm. increased, but did not affect the spontaneous secretion in nine. The secretion was stimulated by the subcutaneous injection of 0.1 mg./10 kg. histamine in four of

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six tests. Free hydrochloric acid was unchanged or increased in seven of nine tests of spontaneous and in all of six, histamine stimulated secretion patients. The same response occurred with ulcer patients as with others.

Since some of the antihistaminic agents are locally anesthetic, it has been considered that their effect was more anesthetic than antihistaminic. Halpern and his colleagues⁵³ recently studied the relative local anesthetic power of Antergan, Neo-Antergan, Phenergan and several other RP substances by measuring corneal sensitivity, using cocaine anesthesia as a standard. Antergan was found to be equal in anesthetic power to cocaine, Phenergan was three times as potent, and other RP compounds, much more so. Neo-Antergan, however, had no anesthetizing power. No constant relationship was discovered between the anesthetizing and the anti-histaminic properties.

ANTISTINE

Antistine, being one of the earlier antihistaminic agents, has been the basis of a great deal of experimental work, both in and out of the field of allergy. Linde⁵⁴ showed that the gastric secretion elicited in anesthetized dogs by the administration of histamine was effectively inhibited by doses of 0.1 gm. of Antistine intravenously, with pre-treatment with Tween 20 administered intravenously at the rate of 1 mg./kg. of body weight per hour. No such inhibition occurred when the administration of Tween did not precede that of Antistine.

Ashford⁵⁵ demonstrated that the subcutaneous administration of 100 mg. of Antistine in normal saline, alone, or fifteen minutes before or fifteen to thirty minutes after the subcutaneous administration of 1.5 mg. of histamine acid phosphate in ten healthy subjects did not lower the concentration or output of hydrochloric acid or pepsin, and in some cases, increased them. No reduction in gastric secretion or clinical improvement occurred in two patients with gastric ulcers given 100 mg. of Anthisan orally three times a day for seventeen and twenty days, respectively. One patient became worse. Similar experiments were done with Benadryl (50 mg.), with equivalent results.

With the present interest in desoxycorticosterone, an experiment showing its effect and that of antihistaminic drugs on histamine shock is of special interest. Gross⁵⁶ removed the adrenal glands of guinea pigs in two sessions, keeping the animals alive after the removal of the second gland by the subcutaneous injection of 25 mg. of a suspension of desoxycorticosterone crystals, the dose being repeated every five to six weeks. In total, fifty-two animals were operated upon, with a mortality of 20 per cent within the first week after complete adrenalectomy. Histamine, given as a 2 per cent aerosol, caused dyspnea and later, coma. At this stage of the experiment the animals were removed from the bell-jar in which they had been kept and usually recovered. Additional doses of desoxycorticosterone acetate (25 mg./kg.) given one hour before the histamine did not prevent the development of bronchospasm in the adrenalectomized animals, but Antistine, 3 mg./kg., did. In normal animals, desoxycorticosterone, in oily or water solution (10 mg./kg.) did not prevent bronchospasm caused by histamine aerosol.

Staub,⁵⁷ one of the first workers in this field, used Antistine in an experiment concerned with epinephrine-histamine regulation. The fact that after the intravenous injection of epinephrine there is a rise in the histamine content of the blood formed the basis of a study of ten patients in whom the antihistaminic effect of Antistine was determined. Antistine in the 200 mg. dose was injected intravenously and then nine minutes later, 0.2 mg. of epinephrine was injected by the same route. The course of the pulse rate and systolic and diastolic blood pressures were then carefully followed, with estimations of blood histamine, using Code's method on the isolated guinea pig ileum. The mode of action of antihistaminic agents had previously been explained

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by Halperin as either depending on the inhibition of histamine formation, an acceleration of the destruction of histamine, or the lack of effect of the histamine present on the cells. Staub believes, however, that Antistine acts by inhibiting histamine formation. The antagonistic action of antihistaminic compounds to exogenously produced histamine leads to a displacement of histamine from the receptor cells and the experiments explain the adrenergic effect of these compounds. An antagonistic effect cannot be demonstrated *in vitro*, because the procedure for the estimation of histamine destroys the antihistaminic compound. *In vivo*, however, there is very little histamine production after the administration of Antistine, probably because the drug prevents either the entrance or exit of histamine from cells and cell surfaces.

Of special importance, if corroborated, is the paper by Stavraky,⁵⁸ who investigated metallic compounds as possible activators of histaminalytic agents. He discovered that while potassium and calcium were ineffectual, ferrous sulfate increased the effectiveness of small doses of Antistine in counteracting blood pressure changes induced by histamine, injected into decerebrated vagotomized cats. Further experiments on eight patients with seasonal hay fever and asthma due to ragweed pollen showed that the administration of calcium and potassium, given in conjunction with such drugs was ineffectual, although ferrous sulfate by mouth in daily doses of 20 to 45 gr., added to Antistine or to Pyribenzamine was most effective in alleviating the allergic manifestation, relieving as well the lassitude and drowsiness seen in side reactions. When ferrous sulfate was given, the doses of Antistine and Pyribenzamine could be increased. The iron compound was given with calcium, in order to reduce its toxicity, since some patients took 0.5-0.6 gm. of ferrous sulfate four or five times daily. It is interesting to note that one patient, in spite of having taken 600 mg. of Antistine daily, developed bronchial asthma, which was not materially helped by epinephrine in oil. When given the iron therapy in addition, he was relieved from asthma within forty-five minutes and was able to continue in comfort throughout the remainder of the pollen season.

The use of Antistine in ophthalmic conditions suggested a study of its toxicity. Schlaegel⁵⁹ instilled 0.5 per cent solution of hydrochloride repeatedly in ten human eyes, producing no discernible corneal damage. Bulbar congestion and subjective stinging were slightly greater with Antistine than with control solutions. Antistine applied to the completely denuded rabbit cornea demonstrated that 0.25 and 0.5 per cent solutions did not delay healing longer than did the control solution. The 1 and 2 per cent solutions, however, were definitely toxic. The 0.5 per cent solution, applied as drops twelve times daily to the eyes of ten human volunteers, failed to affect the size of the pupil or the accommodation. Animal experiments by Yonkmann and his colleagues⁶⁰ showed that 3 drops of 0.5 or 1 per cent solution of Antistine instilled into the eyes of rabbits, delayed or abolished the wink reflex for twenty to thirty minutes. Three successive applications of 3 drops of 0.5 or 1 per cent solution of Antistine or of Pyribenzamine, at three to five-minute intervals into the eyes of six subjects, produced anesthesia of the conjunctiva in ten to fifteen minutes. No pain, hyperemia or pupillary changes occurred.

Hurwitz⁶¹ described the use of Antistine in isotonic solution for the treatment of forty-two to fifty patients with ocular allergy, in which the drug gave moderate to complete relief for the itching, photophobia, lacrimation, conjunctival injection, blurring of vision, secretion and general ocular irritability. The greatest improvement was shown by twenty-three patients with hay fever, with or without other allergic or pathological conditions. Seven of eleven patients with ocular allergy without hay fever improved, the four who failed to improve being sensitive to house dust. Four patients with vernal catarrhal conjunctivitis achieved symptomatic relief and varying degrees of improvement were described as well in nine of twelve patients with palpebral dermatitis, urticaria, eczema, and angioneurotic edema. In some patients, the instillation of the solution was supplemented by application of

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Antistine ointment, the use of moist packs of the solution, and oral administration of 300-400 mg. in tablet form. A number of conditions, including hordeola, chalazions, ulcerative blepharitis, and acute conjunctivitis, did not respond until antibiotic or chemotherapy had resolved the superimposed pathological conditions. The side effects were limited to momentary smarting, and in one instance, a hollow sensation of the eye. Grossman and Loring⁶² proved the solution useful in nodular episcleritis, having treated twenty-two patients suffering from acute attacks with topical instillation, giving three times daily. Three patients obtained subjective relief in twenty-four hours, eleven in twenty-four to seventy-two hours, and seven in three to seven hours. Only one was not relieved. The redness and nodular elevation of the eye subsided in a few days after symptomatic relief began. Daily and Daily⁶³ confirmed these studies using the combination of 0.5 per cent Antistine with 0.015 per cent Privine, instilled as drops into the conjunctival sac of 100 patients for a number of ocular conditions, including blepharospasm, kerato-conjunctivitis sicca, scleritis, episcleritis, and irritation following trauma. The patients showed a rapid decongestion of the conjunctiva with alleviation of the subjective and objective symptoms.

Antistine has been found useful in the treatment of migraine, Biro⁶⁴ finding it to be as effective as ergotamine in arresting migraine attacks. His report states that the drug can be given orally, subcutaneously, intramuscularly, and intravenously during the periods when the patient is symptom-free. Of eleven patients so treated, nine remained free from attacks and in two others the attacks became less frequent, with no toxic reactions being noted.

Of interest is the report by Timonen and Zilliacus⁶⁵ on the use of the Antistine on twelve patients with allergic dermatoses and sludged blood as shown by small red blood cell aggregations in the conjunctival vessels. Of these patients, seven were given 50 mg. heparin intramuscularly four times daily, or initial intravenous doses of 100-150 mg. followed by 50 mg. intravenously four times daily to a total of 50-1500 mg. Three patients were given 0.1 gm. Antistine intramuscularly or intravenously, followed by 0.005-0.1 gm. orally three times daily, one patient receiving oral doses only. Heparin relieved both the aggregations and, except in one case, the dermatitis, but cutaneous relapses occurred in three instances. The Antistine produced a decrease in the rate of aggregation during treatment to a lesser degree than Heparin, and in most cases, the dermatosis decreased or disappeared. In one thirteen-year-old patient with a dermatosis of two years standing and relatively abundant aggregation, the initial intramuscular dose of Antistine produced a clear diminution of the aggregation within fifteen minutes and in six days, during which time 0.05 gm. was given three times daily orally, the skin condition practically clearing. The sedimentation rate was not affected. In one patient, who was not improved with Antistine, there was swelling of the wrists and face, with a decrease in urinary output. These symptoms subsided when the drug had been withdrawn.

Brack⁶⁶ used Antistine for a period of eighteen months in more than 100 patients suffering from urticaria, eczema, neurodermatitis, prurigo, lichen ruber planus, psoriasis, and nervous pruritus, without skin changes, as well as in scabies. He stated that it was occasionally necessary to use doses which caused temporary mild dizziness, in order to have complete suppression of the pruritus. In urticaria, not only was the itching suppressed, but the skin changes were counteracted or prevented. Direct influence upon the skin could not be proven, however, in eczema and neurodermatitis, prurigo and other skin defects, but the indirect therapeutic effect was considerable because the suppression of the pruritus facilitated the effectiveness of other treatment. A parallel study with Antergan showed it to have numerous undesirable secondary effects. The Antistine seemed to suppress the pruritus, regardless of whether the itching was due to sympathetic or parasympathetic factors, indicating to the authors that pruritus was not always produced by H substances.

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Kallós⁶⁷ used Antistine for the same condition, and in addition, for serum sickness and drug exanthemata, as well as for migraine and Ménière's disease. He found that it had little effect in bronchial asthma or migraine. The toxicity was slight and the drug could be used orally, intramuscularly, intravenously, or applied directly to the mucous membranes of the eye and nose. Good results were achieved in vasomotor rhinitis, angioneurotic edema and urticaria, with poor results in asthma. The side effects were seen in thirteen patients but persisted in only seven on the maintenance dose necessary. Because the majority of the patients with urticaria were women, and in several cases the symptoms were aggravated in connection with the menses, it was suggested that in them there might be an endocrine relationship.

Antistine has been found useful in contact dermatitis. Cunz⁶⁸ described "anaphylactic shock" following patch tests with various materials including ammonium oxalate, nicotine and suspension of tobacco dust on a patient with contact dermatitis. An intragluteal injection of Antistine in the 0.1 gm. dose caused a rise in blood pressure, normal respiration and the cessation of vomiting within fifteen minutes. Hughes⁶⁹ reported good clinical results in nineteen of thirty-two patients with bronchial asthma, allergic coryza, eczema, contact dermatitis, urticaria, pruritus or blepharitis. The patients received 100 mg. of Antistine every three to four hours, some of the patients being treated with the same drug subcutaneously. Eighteen per cent of the patients reacted with headache, dizziness, or nausea, but the reactions were seldom sufficiently severe to warrant discontinuance of treatment. Hughes feels that the drug is more useful in acute than in chronic conditions. Britton⁷⁰ used Antistine similarly in fifty-four patients, of whom thirty-eight were improved, twenty-four markedly, and fourteen moderately. The patients were given two 0.1 gm. tablets daily, one on arising and retiring, and if there were no side reactions, the dose was gradually increased to a maximum of two tablets, four times daily. His patients suffered from the following conditions: hay fever, urticaria, vasomotor coryza, pruritus ani, allergic conjunctivitis and migraine. All of the patients relapsed when the drug was withdrawn. Toxic reactions—nausea, drowsiness and headache—occurred in twenty patients, being sufficiently severe to warrant cessation of treatment in seven. Antistine was found effective in some patients who suffered severe side reactions with other antihistaminic drugs and vice versa. Britton feels that the first dose, or any increase, should be given at a time when the patient will not be called upon to perform skilled movements, depending upon acts of judgment, as, for instance, driving an automobile.

The return of symptoms upon cessation of therapy is sometimes accompanied by the additional syndrome of withdrawal symptoms, as described by Cherry,⁷¹ whose report is concerned with labyrinthitis as experienced in three patients, who suddenly ceased antihistaminic therapy, after taking the drugs for prolonged periods of time. One patient took Antistine, another Anthisan, and a third, Benadryl. Administration of one tablet of the responsible drug relieved the symptoms within two hours, but desensitization with decreasing doses of the responsible drug required two and six weeks in the first and second patients and a very short period of time in the third.

The indications for the administration of Antistine, based on the experience of treating eighty-seven patients, are listed by Overton⁷² as the presence of urticaria, angioneurotic edema, eczematous conditions with edema, and itching. He administered increasing doses of the drug until the therapeutic effect, or toxic manifestation occurred, or until 800 mg. was being taken daily, as given locally, orally or intramuscularly. He reports beneficial results in twelve of thirteen patients with chronic constitutional eczema, one with varicose edema, three more with constitutional eczema, four with sensitization dermatitis, one with dermatitis herpetiformis, one with lichen obtusus corneous, two of four with lichen planus, one with mycosis fungoides, two of four with senile pruritus and thirteen of sixteen with chronic urticaria. The drug was without effect in two patients with actinic dermatitis, three with cheiropompholyx, eight with infantile eczema, two with erythema muliforme, two with pem-

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phigus vulgaris, one with psoriasis, fourteen with pruritus ani or vulvae, and six with urticaria papulosa. The side reactions included dizziness and light-headedness in ten, vomiting in one, convulsions in one, collapse in one, disorientation in one, and local induration and soreness after injection in three patients. The doses for children were not over 200 mg. daily. The author concludes that although both drugs are therapeutically equivalent, Antistine causes fewer side reactions than Benadryl.

Hudson⁷³ chose for his clinical trial with Antistine, those patients who were unaffected by Benadryl or Pyribenzamine or who had to discontinue treatment because of the side effects. Of twenty-one patients given Antistine, only one patient suffered from double vision and this was relieved by reducing the dose to below 200 mg. four times daily. The best results were obtained in eight patients with urticarial disorders, all of whom were markedly improved. Of four patients with atopic dermatitis, however, only one completely cleared, but there was a reduction in pruritus of the other lesions. No patients with the pruritus ani or erythromelalgia were relieved and in only two patients with senile pruritus was there moderate improvement. In two cases, the drug was given intravenously with excellent results.

Studies in this country by Kaplan and Eltrlich,⁷⁴ on ninety-five patients given 100 mg. of Antistine three or four times daily for seven to 133 days, showed thirty of thirty-nine patients with hay fever, eight of nineteen with allergic rhinitis, and sixteen of twenty-two patients with bronchial asthma reporting excellent or good results. Three of four patients with chronic urticaria and two of four with atopic eczema and one of two with contact dermatitis reported poor results. The untoward reactions, including nausea, sneezing, dryness of the mouth and dizziness in thirteen patients necessitating discontinuation of the drug in only one.

The pruritus treated need not be of typical allergic origin as shown by the report of Gross⁷⁵ who administered Antistine for four to five days in sixteen children with varicella, superimposed upon tuberculosis. The drug suppressed the pruritus and caused a general improvement, weight gain and prevention of secondary infection. The course of the disease was shortened, the average duration of fever being 2.8 days in treated children as compared to 5.5 days in the untreated controls. The average duration of the exanthemata was 2.8 days for the treated patients as compared to 6.4 days for the control patients. The fever curve was steeper and shorter in treated patients, the peak, however, being above that of the controls. There was no detectible exacerbation of the tuberculosis.

Levin and his colleagues⁷⁶ compared Antistine with Neo-Antergan in the treatment of ragweed hay fever. One hundred and thirty-four patients were divided into three groups; the patients in the first receiving no pre-seasonal or co-seasonal desensitization. Twenty-seven of these were given Neo-Antergan and reported 70 per cent relief, while twenty-three were given Antistine and reported 65 per cent relief. In the second group, ragweed desensitization was given, and in addition, Neo-Antergan in fourteen, giving 79 per cent relief, while Antistine was administered to twenty, effecting 75 per cent relief. Of the third group of patients who received ragweed desensitization alone, of fifty patients, 76 per cent were relieved. Of the total of forty-one patients treated with Neo-Antergan, 36 per cent had one or more toxic reactions, whereas of the forty-three treated with Antistine only 21 per cent reported side effects.

Dickstein⁷⁷ substituted Antistine for Benadryl or Pyribenzamine during the height of the ragweed season, giving doses of 100-200 mg. to eight adults and nine children, in whom hay fever symptoms were present at a pollen count of 500 or more. All of the patients were under ragweed desensitization therapy, 88 per cent reporting satisfactory relief with 25 mg. of Pyribenzamine and 64 per cent with Benadryl. The side effects were listed as listlessness and nausea in 60 per cent of the patients, being severe in 18 per cent of the patients given Pyribenzamine. Grogginess and sleepiness occurred in 47 per cent of the patients and was severe in 29 per cent of those given

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Benadryl. Antistine gave satisfactory relief in 20 per cent of the patients. Side effects of nausea, listlessness and vomiting occurred in 18 per cent, being objectionable in only 6 per cent. It was noted that of three patients who obtained relief with Antistine, two were children, aged three and three and one-half, respectively, and another was a patient with a very high sensitivity to all drugs. Although the children received relatively high doses, none had unpleasant side effects.

Walton⁷⁸ compared Antistine with Neo-Antergan and Pyribenzamine, finding 50 mg. of Pyribenzamine equal to 100 mg. of Antistine. Toxic reactions occurred in 25 per cent of the patients receiving Antistine and in 27 per cent of those given Pyribenzamine. Marked relief of perennial hay fever occurred in four of five patients given 100 mg. of Neo-Antergan. The drug caused a severe exacerbation in one asthmatic patient, but no other toxic reaction. It was successful in two patients who did not respond to the other drugs. Antistine is credited as causing improvement in fifty-one of eighty-three patients, while Pyribenzamine improved twenty-one of twenty-six patients. The conditions treated included seasonal or perennial allergic coryza, asthma, urticaria, atopic dermatitis or migraine.

Using Antistine alone, Friedlaender and Friedlaender⁷⁹ reported benefit in nine of twenty-four patients with bronchial asthma, thirty-five of fifty with vasomotor coryza, seven of ten with acute urticaria, three of nine with chronic urticaria, one of six with allergic headache, three of five with atopic dermatitis and three of six with contact dermatitis. The drug neither benefited patients with penicillin urticaria, pruritus ani, nor with unclassified dermatitis. The average dose was 50 to 100 mg. four times daily. A clinical comparison showed that, in general, 100 mg. of Antistine was as effective as 50 mg. of Pyribenzamine. Of eleven patients with allergic conjunctivitis treated with instillation of the 0.5 per cent solution, eight experienced symptomatic relief.

Comparative studies involving Antistine and other drugs have been written by Arbesman,⁸⁰ Waldbott and Young⁸¹ and Gay and his colleagues.⁸² Arbesman studied 291 patients suffering from allergic coryza or bronchial asthma, or both. The patients were carefully interviewed at definite intervals, recording their symptoms each day on special cards. A patient was regarded as improved when he had at least 50 per cent relief of his symptoms. Patients were given Antistine, Neo-Antergan and Neohetramine, in 100 mg. doses, Pyribenzamine in 50 mg. doses and Hydryllin (Benadryl, 25 mg.; aminophylline, 100 mg.) in doses of one or two tablets. The patients took the drugs only when required, the daily dose not being stated. Eighty per cent of the patients with allergic rhinitis treated by Pyribenzamine reported their conditions improved and 63 per cent of those taking Neo-Antergan. The other drugs had lesser effects. In bronchial asthma, Hydryllin was effective in 64 per cent of forty-eight patients, with Neo-Antergan effective in 43 per cent and Pyribenzamine in 45 per cent. The lesser potent substances, Neohetramine and Antistine, caused fewer side reactions, although they proved markedly effective in certain patients. Waldbott and Young's patients were given Antistine, Benadryl, Neo-Antergan, Neohetramine, Phenergan and Trimeton. In all, 395 patients were treated, as suffering from hay fever and allergic coryza, urticaria and angioneurotic edema, as well as bronchial asthma. The author reports that the six drugs acted similarly in the degree of relief afforded. The variation and duration of the effect was related to the severity of the condition rather than to the drug used, excepting in Phenergan, which decidedly had a more protracted action, although dizziness and drowsiness were more pronounced with this drug than with any of the others, excepting Benadryl. Since the therapeutic effect outlasted the soporific action by several hours it was used with greatest advantage at bedtime.

The study by Gay includes 686 patients treated with Antistine, Chlorothen, Histadyl, Hydryllin, Neo-Antergan, Pyribenzamine, a drug termed Compound 1913 (described as Compound 1721 in addition to aminophylline). Of 428 patients with

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seasonal perennial allergic rhinitis, the drugs benefited an average of 68 per cent, Pyribenzamine helping 75 per cent of 51, Hydryllin 73 per cent of ninety-seven, Antistine 70 per cent of forty-three, and Neo-Antergan 70 per cent of 102. Although nasal obstruction was seldom influenced, the itching of the eyes and nose, the watery discharge and sneezing were relieved. In fifty-three cases of urticaria, Antistine relieved seventeen of nineteen, Hydryllin eight of ten, and Neo-Antergan six of ten, the average being 77 per cent. In fifty-six cases of dermatitis and pruritic conditions of varying origin, Antistine helped twenty-one of twenty-nine patients, and Histadyl nineteen of twenty-seven patients. Severe bronchial asthma required epinephrine and aminophylline and only 40 per cent of ninety-six mild cases responded at all to histaminalytic agents. Gay notes, as have others, that ragweed-hay fever patients, who responded well in the previous season, contracted severe asthma in unusual numbers at the end of the season and could not be helped at all. The side reactions totalled 13 per cent of 110 patients given Antistine and 42 per cent of twenty-six patients given Compound 1913. Histadyl had the second lowest frequency of side reactions (19 per cent). One hundred and nineteen patients complained of drowsiness, the other side effects noted being dizziness, weakness, fatigue, headache, nervousness, tremor, apprehension, tachycardia and anorexia, nausea, abdominal pain, diarrhea, dryness of the mouth, blurred vision, dysuria and urinary frequency. Severe side reactions occurred with 18 per cent of 142 patients given Hydryllin, and 25 per cent of seventy-one patients who took Pyribenzamine. The critical dosage of Antistine was discovered to be 400 mg. daily, while that of Hydryllin was 100 mg. and that of Histadyl, 200 mg.

Late in 1945, McElin and Horton⁸³ published the earliest report on the use of Benadryl in eighty-one patients, describing it as giving excellent results in thirty-seven patients, with good results in eleven others suffering from allergic conditions not amenable to any other form of treatment. Twenty-one of twenty-two with seasonal hay fever achieved 50 per cent relief and nineteen obtained 75 per cent or greater relief. Three patients with Ménière's disease were completely relieved within twenty-four hours. Three patients allergic to penicillin, and a fourth, allergic to the barbiturates, obtained relief from pruritus in two to four minutes, with the lesions disappearing in eight in twenty-four hours. Patients with recurrent contact dermatitis, trigeminal neuralgia, physical allergy, characterized by irritation of the eyelids and photophobia showed only slight improvement. Intravenous injections were given to patients with dysmenorrhea, hay fever, vasomotor rhinitis, and histaminic cephalgia, all being relieved rapidly in some, in thirty seconds. In an epileptic patient intravenous administration of 60 mg. aborted an attack. Sleepiness, dizziness, dry mouth and nervousness occurred in ten of the seventy-four patients who received Benadryl orally. Other side effects noted were frequency, fatigue, epigastric distress, inco-ordination, nausea, bad taste, bleeding tendency, sense of relaxation, diarrhea, constipation, excessive perspiration, tinnitus and blurring of vision. One patient developed a generalized pruritus.

In Logan's series⁸⁴ there were eighteen children, the dose being 2 mg./lb./day given in two to four doses. If there was no result in thirty to forty minutes, the dose was considered inadequate. In a two-year-old child, a 10 mg. dose effected disappearance of hives within thirty minutes, with relief being maintained while treatment was continued. Benadryl was also used before plasma infusions, obviating reactions, as well as in the treatment of the generalized urticaria and swelling due to tetanus and gas gangrene antitoxins. The only toxic symptoms seen were drowsiness and vomiting, and local anesthesia of the tongue.

Feinberg and Friedlaender⁸⁵ administered 50 mg. of Benadryl five hours, three hours and one hour before skin-testing thirty dermatographic patients, with temporary partial or complete control of whealing. The drug, however, did not prevent specific skin reactions to all allergens, including pollens, fungi, house dust, danders and some

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foods. No improvement was noted in twelve patients with allergic rhinitis, seventeen with asthma or two with chronic urticaria, while two other patients with chronic urticaria obtained almost complete relief.

Studies on sixty normal and 242 allergic individuals were initiated by McGavack et al.⁸⁶ It was discovered that Benadryl suppressed the dermal response to histamine in both types of patients, depressing the gastric acidity in twenty of twenty-one subjects, decreasing capillary permeability and lowering the systolic blood pressure of twenty-nine of seventy-four patients by 10 mm. or more when 250 to 600 mg. of Benadryl were given for twenty-one to 280 days. Glucose tolerance was increased following 20 mg. given intravenously. Benadryl also exerted an atropine-like activity on the eyes of forty-three of sixty subjects when the 0.5 per cent aqueous solution was applied. Fewer than half of the patients with eczema and neurodermatitis were benefited, but 60 per cent of the patients with bronchial asthma, hay fever, vaso-motor rhinitis, allergic hydroarthrosis, functional dysmenorrhea, spastic colon, migraine and Ménière's syndrome were helped. The drug was less effective when used for treating intractable insomnia, cardiac asthma, hypertension or epilepsy. Of the 242 patients, 131 reported untoward reactions, especially drowsiness. The highest percentage occurred in the patients who required 150 mg./day. Drowsiness, however, was occasionally seen with doses as small as 50 mg. In five cases, withdrawal of the drug was necessary. Although clinical response usually followed in twenty minutes, it was sometimes delayed twelve to thirty hours.

Bain and his co-workers⁸⁷ measured the effect of Benadryl upon intradermal histamine reactions in eleven men following a single oral dose of 100 mg. Anthisan, in the 200 mg. dose, and Phenergan in the 50 mg. dose, were used for comparison. Benadryl barely reduced the wheal response after three hours, while Anthisan and Phenergan caused significant reductions of the flare and wheals within one hour, the effect lasting twenty-seven and thirty-two hours, respectively. The patients who showed poor specific response to one drug, also showed poor specific response to the others, but responded normally when the doses were increased. Twenty patients with chronic urticaria given Anthisan indicated that the dosage necessary to suppress or modify the wheal was the same as that known to cause modification of urticaria. All three drugs caused side reactions, which were greater with higher doses. Perry and Hearin⁸⁸ used histamine iontophoresis to determine the duration of antihistaminic activity of orally-administered compounds. Their normal subjects included nineteen males and twenty-six females, varying in age from nineteen to forty-three years. The maximum antihistaminic activity of Benadryl, but also of Pyribenzamine and Hydryllin, was reached in two hours after the ingestion of each of the three drugs in thirty-seven patients; and three hours in the remaining eight, probably because of slow absorption. The effect had completely disappeared in five hours in all but two subjects, and almost so in these.

Since histamine stimulates the secretion of hydrochloric acid, it was logical to theorize that an antihistaminic agent would inhibit the process and would, therefore, be useful for the treatment of peptic ulcer. In animals, such an effect has not been consistently seen. There are some reports in the literature and oral antihistaminic therapy has relieved peptic ulcer symptoms. These, of course, may be due to the anesthetic effect of the drug, or may be coincidental results. In any case, Gilg⁸⁹ reported that 50-100 mg. Amidryl (Benadryl) resulted in an increased reaction to subcutaneous injection with 0.5 mg. histamine in nine patients, increasing the volume, the free acid and the total acidity of the gastric secretion. Administration of the solution of Amidryl directly into the stomach in the absence of histamine resulted in increased gastric secretion, or increased acidity in four individuals. Gilg believes that Amidryl acted as a synergist with histamine in the original experiment. Alsted⁹⁰ gave Amidryl (Benadryl) to twenty patients with gastric or duodenal ulcer. Thirteen received 400 mg. of Amidryl daily for four weeks and seven received antacid

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therapy. Following the administration of 0.5 mg. of histamine, gastric secretion was suppressed in six of the Amidryl patients and remained unchanged in four. Results in three patients were inconclusive. No such depression of gastric acidity was observed in seven patients treated with antacids.

McGavack, et al⁹¹ determined the levels for Benadryl in blood and urine following a single oral administered dose. The blood values began to rise within sixty minutes and reached an average peak of 1.07 micrograms/c.c. between ninety and 120 minutes. Pyribenzamine used as a comparison showed an appreciable rise, first evident at 120 minutes, with the trend still upwards at 180 minutes. Within the first twenty-four hours, 46.0 and 20.1 per cent of the ingested Benadryl and Pyribenzamine, respectively, were excreted in the urine.

In 1947, there were a number of reports of patients who developed hypertension during the administration of Benadryl. Gelfand⁹² described a hay fever subject whose pressure rose from 138/85 to 200/110 following its ingestion. A colleague informed the author that he had had two similar cases. Mackmull⁹³ injected fifty patients with intravenous Benadryl in doses of 50, 75, 100, 200 and 300 mg. The average systolic and diastolic blood pressures were elevated after all, particularly with the doses of over 100 mg., although none of the patients were hypertensive. The use of large intravenous doses of Benadryl is contra-indicated in the presence of hypertension. Electrocardiographic changes of sufficient significance occurred after the 200 and 300 mg. doses to preclude the use of such treatment in patients with heart disease.

Reinstein and McGavack⁹⁴ performed standard glucose tolerance tests on 17 subjects who were maintained on a basic diet for 3 days before the first test and throughout the entire period of study, excepting on the days when the tests were taken, three tests being performed on each subject. Benadryl intravenously was shown to cause a significant increase in sugar tolerance in all patients, irrespective of age. In order to rule out any normal variation in glucose tolerance when determined at three-day intervals, three subjects were given the same regime as the fourteen test subjects mentioned, excepting that no medication was used in conjunction with any of the three tests on those subjects. These same authors⁹⁵ have recommended that Benadryl be used in doses of 50 mg., three times daily, increased by 50 mg. every day until symptomatic relief is obtained, stating that up to 600 mg. daily can be given safely by this method. The minimum effective doses continue for two weeks. They state that side reactions can often be eliminated by starting with smaller doses and giving the drug during or immediately after meals, with tolerance usually establishing itself with twenty-four to ninety-six hours. Of 313 patients suffering from various allergic conditions and related diseases, 141 obtained complete relief and seventy-eight were improved after Benadryl treatment which lasted for two weeks in acute cases; for one year in chronic conditions. Zolov⁹⁶ treated his patients with a 10 to 25 mg./c.c. dose given intravenously during two minutes, on one or more occasion, one of his twenty-six patients receiving a 30 mg. in 100 c.c. of saline over a ten-minute period. Good to excellent results were seen in all but six of fourteen patients with bronchial asthma, and all but one of four with ragweed hay fever, three with vasomotor rhinitis, two with neurodermatitis, and one each with poison ivy, angioneurotic edema and dermatitis medicamentosa. In three of the patients with acute bronchial asthma and hay fever, relief occurred in five to fifteen minutes, the patients remaining free of symptoms for three to four hours. The poison ivy pruritus was relieved for six hours. The reactions included nausea in one patient following a 15 mg. injection, intense headache beginning in one hour after a 20 mg. injection, the symptoms lasting twelve hours. A third patient suffered chills beginning one hour after the injection and lasting for thirty minutes.

In 1946, Slater and Francis⁹⁷ described Benadryl as a contributing cause of an accident. The patient, who drove an electric cargo platform truck, lost control of

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the machine and jumped clear, following which it went off the platform and was wrecked. Reports of unusual side reactions began to appear in rapid succession. Borman's case⁹⁸ suffered from mental lethargy, mental confusion and disorientation. Weil's case⁹⁹ responded with muscular epileptiform twitching, slurring of speech, inco-ordination and nervousness as manifested by singing and laughing during normal sleeping hours, following 100 mg. doses, the 50 mg. dose causing no symptoms. The patient described by Geiger et al¹⁰⁰ responded to Benadryl with pallor, low blood pressure and a general shock-like reaction with diminished vision, drowsiness and pyrosis. The length of time reactions can occur was demonstrated by a patient of Schwartzenberg and Willerson,¹⁰¹ who responded to Benadryl with neuritic and gastrointestinal symptoms, paller, drowsiness, general malaise, an inability to co-ordinate thought and speech, and numbness and tingling in the extremities. The patient had taken twenty-three capsules of 50 mg. each in twenty days, the reactions lasting approximately three months. Duerfeldt's patient,¹⁰² a three-year-old child, took 700 to 800 mg. of Benadryl accidentally. Symptoms of nervousness and muscular twitching occurred within fifteen minutes, followed by convulsions and respiratory collapse. Among other things, the patient was given Dilaudid (2 mg.) and histamine, 3 mg. Asthmatic rhonchi were noted in forty-five minutes after the histamine was administered and repeated doses of epinephrine (0.1 c.c.) were required to control the asthmatic breathing. The convulsions were finally controlled with 30 c.c. of 50 per cent ether in oil administered rectally, the ataxia gradually decreasing by the fourth post-treatment day. Duerfeldt also mentions a teen-aged girl, who took thirty of the 50 mg. capsules with a successful suicidal intent. Sands¹⁰³ describes acute gastric and renal irritation lasting forty-eight hours in a patient following the oral administration of six Benadryl capsules in three days, and Swartz¹⁰⁴ reports tinnitus, vertigo and nystagmus in a thirty-two-year-old patient who took 550 mg. of Benadryl in six days. His symptoms subsided on the seventh day of treatment with ephedrine and ammonium chloride. They were reproduced on two subsequent occasions by administration of small amounts of Benadryl in elixir and powder form. Convulsions, protrusion of the tongue, bulging eyes, cyanosis and threshing movements of the arms and legs developed in a normal child one-half hour after the accidental ingestion of approximately 50 mg. of Benadryl. Starr and Rankin¹⁰⁵ reported that the patient gradually improved during the next twenty-four hours after gastric lavage and the administration of magnesium sulfate, phenobarbital, and sodium Amytal. The length of time such symptoms may persist is shown by the report of Pereira,¹⁰⁶ whose patient took 300 mg. of Benadryl in three days, developing nausea, vomiting, diarrhea, somnolence, hallucinations, temporary blindness and internal strabismus. The symptoms abated within four days, excepting for those referred to the eye, which disappeared in one and one-half months, with residual hemianopsia in one eye. Impotence, a symptom which may have escaped early observation, was described by Jennes.¹⁰⁷ It followed the use of Benadryl, Pyribenzamine and Thephorin in one patient, although Benadryl caused no such effect in the second patient. A complete review of the toxicity of Benadryl has been assembled by Sachs.¹⁰⁸ A reprint or photostat copy should be in the hands of every allergist who prescribes antihistaminic agents. The following list, repeated for emphasis, includes all the effects culled from the literature by Sachs and mentions a number of others since reported upon. It should be noted that these reactions are of the more obviously superficial functional type. Long range studies have not been done for possible deep-lying changes which only time and investigative perspicacity may uncover. The reactions so far known vary from slight drowsiness, at the best, to fatal toxicity, at the worst. The greater number of reactions are neuro-psychiatric and all of the following have been described: drowsiness, dizziness, faintness and fainting attacks, mental confusion, difficulty in co-ordination, disorientation, narcolepsy, stupor, coma, giddiness, general hallucinations, apprehension, nervousness, weakness, fatigue, head-

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ache, amnesia, lassitude, choking and slurred speech, somnambulism, exhaustion, irritability, athetoid movements, spastic jactations, acute melancholia, suicidal tendencies, peripheral neuritis, bilateral tinnitus, insomnia, tremor, sense of relaxation, mental lethargy, "walking on air," acute hysteria, jerky and rapid speech, and "an all gone feeling at the pit of the stomach," as well as a generalized numbness. In the ocular system, patients have complained of photophobia, dimming of vision, dilated pupils, difficulty in accommodation and blurring of vision, as well as visual hallucinations, and rapid nystagmus. There may be complaints of muscular aching and twitching, low back pain, genito-urinary symptoms such as impotence, incontinence, frequency and bladder discomfort. In the respiratory and alimentary tracts, the patient may complain of a dry nose, dry oral cavity, olfactory hallucinations, bad taste, "chloroform-like taste," nausea, vomiting, epigastric distress, indigestion, pyrosis, sore tongue, abdominal cramps, diarrhea or constipation. In some patients, ingestion has caused bronchial asthma and also respiratory arrest requiring artificial respiration. In the cardiovascular system, the response has been vasospasm of the fingers with pallor, hot flashes, shock-like reaction and chills, as well as excessive perspiration, or cold extremities, orthostatic hypotension, true hypotension, facial edema, elevated pulse rate, palpitations and a tendency to bleeding. Aggravation of the original symptoms has been seen, as well as generalized pruritus and urticaria. Skin manifestations following the ingestion of antihistaminic agents include eczematoid dermatitis, pityriasis-rosacea-like reactions and erythematopapular eruptions.

Comparative studies of the toxic manifestations of Benadryl and Pyribenzamine have been done by McGavack et al,¹⁰⁹ some reactions occurring in forty of the fifty-two patients who received only Benadryl, and thirty-five of fifty-two receiving Pyribenzamine. The most common symptoms noted were drowsiness, oral dryness, dizziness, weakness and nausea. A tendency to establish tolerance was more evident with the former rather than the latter drug, but at dosage levels of 300 mg./daily, the incidence of reactions was approximately equal. At levels of 450 mg./daily, Benadryl was definitely more toxic. Holtkamp et al¹¹⁰ compared the side effects of Benadryl, Pyribenzamine and Hydryllin in normal college students, the medication being given three times daily with food. It was discovered that by the Bourdon test that there was an appreciably altered mental ability as demonstrated also by the reaction time using an impulse counter and the minimum distance two-point discrimination test. Benadryl heightened the response in twelve subjects, Pyribenzamine in six and Hydryllin in sixteen. Benadryl and Hydryllin also decreased the response in eleven subjects and Pyribenzamine in fifteen. The decreases caused by Benadryl were of greater magnitude than those caused by Pyribenzamine. In two patients the slow motor response was sufficient to incapacitate them, while drowsiness, headache and dizziness occurred after 50 mg. of Benadryl in one patient. Benadryl and Hydryllin tended to lower the systolic and diastolic blood pressures of six subjects and reduce the respiratory rate in seven.

Of the fatalities known, only two have been chosen for description. The patient reported by Blackman and Hayes¹¹¹ died following the second of two oral doses of 100 mg. Benadryl, the acute bronchial asthma being exacerbated, Benadryl causing severe depression of the central nervous system. The same patient had received 50 mg. of Demerol and 1½ gr. of phenobarbital, given with other supportive measures following the appearance of the alarming reaction. The patient described by Davis and Hunt¹¹² had taken a dose of 474 mg. by accident.

All of the reactions so far described are those of oral administration. McGavack et al¹¹³ tested the effects of topical applications, using four different ointment bases and strengths of 2 to 5 per cent in sixty-three subjects. The concentrations listed completely destroy the response of the skin to intradermally applied histamine. Polyethylene glycol monostearate and oil and water emulsions appeared to be the best bases employed. In seventy-four patients with itching dermatitis, forty-four obtained com-

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plete relief and, in addition, eighteen were improved. Six patients experienced discomfort from the application of the ointment, particularly with a 5 per cent concentration. In two patients this was shown as due to the base, and in another, to the aggravation of the weeping eczematous lesions. There were no systemic side reactions.

The use of antihistaminic agents, especially Benadryl, in the treatment of reactions to penicillin has been published in detail in the author's review on reactions to penicillin.¹¹⁴ In brief, the recommendation of Pillsbury et al are followed. The penicillin therapy is discontinued as soon as symptoms occur, and Benadryl or Pyribenzamine given orally three to six times a day in doses of 50 to 100 mg. or 5 to 10 mg. intravenously in 20 c.c. of isotonic saline. The antihistamine drug administration should be continued with amounts decreasing gradually if the response to a new brand of penicillin is good, or increased if urticaria persists or recurs. According to Taplin and Bryan,¹¹⁵ a 1 per cent Benadryl solution can be used with micronized penicillin for the aerosol treatment of patients with intrinsic bronchial asthma, Benadryl causing a reduction in cough and a decrease in sputum in 320 such patients. The micronized Benadryl alone, or mixed with vasoconstrictors, is symptomatically effective in asthma after inhalation of 1/10 to 1/20 the usual oral dose. Only eighteen of the 320 patients treated with penicillin potassium aerosol demonstrated allergic reactions.

The use of Benadryl in streptomycin sensitivity has been described by Holt and Snell,¹¹⁶ whose patient responded with angioneurotic edema and moderate swelling of the lips and face after nine days of treatment. Benadryl in the 50 mg. dose four times daily relieved the condition in twenty-four hours. Bignall and Crofton¹¹⁷ reported that the nausea and vomiting which sometimes followed the use of large doses of streptomycin could be relieved by Benadryl in 50 mg. doses eight hourly, the morning vomiting recurring when the Benadryl was discontinued, ceasing abruptly when Benadryl treatment was initiated. The substitution of lactose capsules was without benefit. Because of the suspicion that the Benadryl might be acting as a sedative, phenobarbital was substituted with no relief. The patient also was relieved by Antistine.

Contact dermatitis due to streptomycin, however, is not affected by Benadryl as described by Cucchiani and Erdstein,¹¹⁸ who treated seven nurses who had been exposed to streptomycin, responding with pruriginous papules and vesicles, fissures, desquamation, exanthemata of the fingers, elbows and eyelids. Antistine was also ineffective.

Benadryl has been used in urticaria due to both liver and insulin. The first, by Nicholson,¹¹⁹ whose patient responded with urticaria following 2 ml. liver extract injected monthly, with 0.3 to 0.5 ml. of epinephrine. The simultaneous administration of 100 mg. of Benadryl permitted the patient to take treatment safely. Leavitt and Gastineau¹²⁰ gave Benadryl orally with complete relief of local and generalized urticaria to an insulin-sensitive patient, the local reaction being prevented by the solution of Benadryl mixed with the insulin. Passive transfer tests revealed the presence of reagins in the patient's serum and direct skin tests gave evidence of the inhibition of Benadryl. With the small dose used (0.5 to 1.0 c.c. of 1:1000 Benadryl) side reactions may be avoided, although in some cases, oral as well as parenteral administration of Benadryl may be necessary to control severe localized or generalized reactions. Exact techniques for the use of antihistaminic drugs in treating patients allergic to liver extract can be found in the reports by Carryer and Koelsche,¹²¹ and for insulin, by Klein¹²².

No review of the antihistaminic drugs would be complete unless mention were made of the numerous non-allergic conditions, which respond to their administration. Among others, convulsive seizures have been treated by Churchill and Gammon,¹²³ who report that a single intravenous injection of 30 to 125 mg. of Benadryl in ten

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patients with true or variant petit mal reduced the spike-wave abnormality as seen in the electroencephalogram, increasing it in two patients with focal discharge, producing motor convulsions in one. The intravenous administration of 8 to 75 mg. of Pyribenzamine to seven patients with petit mal resulted in increased abnormalities in five, but no change in two. Oral doses of 75 to 400 mg. of Benadryl to twelve patients with true petit mal decreased the frequency of attacks in eight, markedly so in four. Oral doses of Pyribenzamine failed to improve the condition of an unspecified number of patients tested, decreasing the generalized seizures in one. The authors urge that antihistaminic drugs should be used with care in treating patients who suffer from convulsive disorders since the drug has been proven to cause attacks. Horton and Brennan¹²¹ discovered that patients with trigeminal neuralgia were benefited by Benadryl in the 100 mg. or Pyribenzamine in the 50 mg. dose. Since atropine and phenobarbital have been ineffective, the authors conclude that Benadryl and Pyribenzamine exerted their therapeutic effects by antihistaminic activity rather than by antispasmodic or sedative reasons. Young¹²⁵ treated a patient with herpes zoster, with 50 mg. of Benadryl every four hours, complete cure occurring in five days. The patient also received 10 units of Pituitrin. MacPherson¹²⁶ used Benadryl in dysmenorrhea, the dose being one capsule, three times daily beginning the day before the expected period. One of his patients was relieved in ten minutes by 1 c.c. of epinephrine 1:1000, the epinephrine being just as effective on the second occasion. Finch¹²⁷ gave twenty-nine pregnant women Benadryl to control their nausea and vomiting. Two of three cases of pernicious, and all of eight cases with severe, vomiting, eleven of twelve with moderate vomiting, as well as all of six with mild nausea and vomiting were completely relieved. Severe cases were given intravenous injections of 50 mg. three or four times daily during the first twenty-four hours, with 50 to 100 mg. orally, three or four times daily, as needed. Another group of patients studied by the same author as suffering from metrorrhagia, dysmenorrhea, or menopausal symptoms treated with diethylstilbestrol with severe vomiting, were able to tolerate it as well as Progesterone and hexestrol when oral Benadryl was given simultaneously. Histadyl was of equal value.

In 1948, Budnitz¹²⁸ reported Benadryl as reducing the severity of symptoms in all of ten patients suffering from Parkinson's disease for two to fourteen years, the dose being 50 mg. four times daily, for three to fourteen months. When the drug was withdrawn and when Pyribenzamine was substituted, the return of symptoms occurred. Tolerance did not develop; larger doses did not produce added improvement, and there was no increase in the benefits over those observed at first when treatment was prolonged. A synergistic action with parasympathetic-inhibitory drugs and Benadryl was observed in four patients who used them simultaneously. Confirmation of this work by Pettit,¹²⁹ by Spickler¹³⁰ and by Gates¹³¹ were soon forthcoming, with a complete report by Ryan and Wood,¹³² who have treated forty patients since 1947. The therapeutic effect was noted to reach its maximum in ten days. The belladonna, if used, must be withdrawn gradually. Complete relapse occurs within forty-eight hours after cessation of Benadryl treatment; two patients in this series had taken 200 mg. daily for over eighteen months with no ill effects.

That Benadryl may be useful in contact dermatitis due to atropine is seen in the report by Fralick and Kiess,¹³³ who had nine patients with atropine dermatitis, the patients also being sensitive to homatropine, scopolamine and duoboisine. The local use of Benadryl and the oral administration of Pyribenzamine made it possible to continue the treatment of the iridocyclitis with no ill effects.

For the control of allergy to antirabic vaccine, Slipyan¹³⁴ administered 50 mg. of Benadryl to relieve the generalized urticaria which developed in a ten-year-old boy who, during prophylactic therapy, was also given 300,000 units of penicillin intramuscularly for two successive days. The allergic reactions reappeared when the Benadryl was withdrawn but responded to subsequent re-administration. Patch tests

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to penicillin and rabies vaccine were positive only for the vaccine. Pickar and Kramer¹³³ used Benadryl in a twenty-six-year-old patient, who developed encephalomyelitis with confusion, disorientation, and circulatory collapse, without paralysis after ten injections of phenol-killed anti-rabies vaccine. A prompt improvement in all symptoms followed the administration of 100 mg. Benadryl intravenously in 1,000 c.c. of 5 per cent glucose saline, in addition to 100 mg. orally four hours later. The drug was continued for nine days when extreme somnolence necessitated its discontinuance. The temperature rose and the symptoms recurred, this time being completely counteracted by 100 mg. doses of Pyribenzamine given three times daily for seven days.

The ends to which physicians will go in attempting to discover conditions for which antihistaminic agents are specific is shown in the work of Wilson¹³⁶ who reports on thirty-eight patients with granular proctitis who had responded to no other therapy. Given 50 mg. of Benadryl three times daily for two to eighteen weeks, benefit was seen in twenty patients with considerable improvement in fifteen more. The author feels that the relief was greater than those attributable to the sedative and antispasmodic effects of the drug, although no antihistaminic action could be demonstrated. In some patients, the nausea present may increase until the patient becomes accustomed to the drug. Benadryl has also been used in infantile gastroenteritis by Neumann¹³⁷ who found that starvation resulted in a reduction of the average number of stools from ten to three and one-half a day, although four of twenty-four infants died. Sixteen babies in the second group received the same treatment; that is, starvation and saline or Hartmann's solution orally or parenterally, with buttermilk and Benadryl in doses of 1 mg. for every month of age every four hours until improvement occurred and then four times daily. The number of stools decreased from eleven to four, although the fever was uninfluenced. The condition of the babies deteriorated when Benadryl was discontinued.

A medical research unit of the U. S. Navy¹³⁸ attempted to measure the efficacy of Benadryl in the therapy of rheumatic fever. No clinical significant improvement nor decrease in the frequency of arthralgia or the incidence of coryza occurred in eight patients given 50 mg. orally every four hours up to 300 mg. daily for the first five days and then 400 mg. daily for the next seven days, and finally 900 mg. daily for nine days. In five patients, mild drowsiness was observed, and blurred vision and dryness of the mouth occurred respectively in seven and five more. The patients demonstrated withdrawal symptoms such as anorexia, nausea, headache, vomiting and facial erythema when treatment was discontinued. Serial histamine flare tests were made on all patients before and at regular intervals during Benadryl therapy to insure effective dosage levels.

It would appear that Benadryl is efficacious in the treatment of polyarteritis nodosa. According to Sutherland,¹³⁹ a patient with a typical clinical picture of this condition given Benadryl alone was not helped. When, in addition, histamine azo-protein was injected, there was no exacerbation from the disease and the patient was able to return to work, his weight remaining stationary and the B.S.R. normal.

In 1945, Williams¹⁴⁰ reported relief from the syndrome of physical allergy of the head, perennial vasomotor rhinitis, myalgia, Ménière's disease and vasodilating pain, as evidenced thirty minutes after the ingestion of Benadryl (50 mg.), the effect lasting about two hours. The average patient could be maintained relatively asymptomatic with Benadryl (300 mg.), given in six divided doses at two-hour intervals. Ten of twelve patients with vasomotor rhinitis were almost completely relieved. Four patients with hyperplastic ethmoiditis obtained marked relief with retraction and disappearance of polypoid tissue and diminution or disappearance of the purulent discharge. The symptoms tended to return within twelve hours after cessation of treatment. Five patients with myalgia reported 40 to 50 per cent relief, and two patients with Ménière's disease obtained 75 to 80 per cent relief. Two patients,

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who refused further treatment, complained of severe vertigo appearing within forty-five minutes. Four patients experienced difficulty in accommodation and many patients complained of drowsiness and extreme nervousness.

In 1947, Goodman and Coonrad¹⁴¹ described the prophylactic effect of Benadryl in experimental histamine headache. In twenty-two of thirty-four individuals subject to headaches of various types, the injection of histamine phosphate (0.3 mg.) induced headaches which could be prevented by Benadryl (100 mg.) given orally one hour before a second histamine injection, the results being 100 per cent effective. In another fifty-four patients, in thirty-one of whom histamine reproduced their headaches, of the eighteen given Benadryl, fifteen responded satisfactorily. The author reported that Benadryl was 92.5 per cent effective in forty patients who had previously developed head pains following histamine injections. Four control cases given a placebo developed headaches on repetition of the histamine injection. Lee,¹⁴² however, reported that Benadryl was unsuccessful in the treatment of histamine headache. Rainey¹⁴³ also in reporting on 121 patients with aural vertigo treated with unspecified intravenous doses of histamine phosphate, noted that Benadryl and/or Pyribenzamine had been given to some patients without effect, and in some cases intensified untoward reactions, although 83 per cent showed excellent results following the intravenous injection of histamine phosphate alone, with 25 per cent of the patients requiring additional courses of treatment.

Benadryl has been used in the treatment of solar urticaria. Beal¹⁴⁴ reported not only that the serum of two patients could be passively transferred to the skin of normal individuals who responded to the ultra-violet radiation, but also that both patients responded to two daily doses of Benadryl, 100 mg. and while thus protected were desensitized by increasing exposures to ultra-violet radiation. Sensitivity to cold has been treated by Notier and Roth,¹⁴⁵ the patients showing a 50 per cent improvement after Benadryl, 50 mg., had been taken four times daily for eighteen days. Gastric distress made it necessary to reduce the dose to 100 mg. daily. Symptoms returned within two weeks after cessation of treatment. Mullinger and Bogoch¹⁴⁵ reviewed the literature and added a case report of a patient hypersensitive to cold, who improved only slightly after taking Benadryl, 100 mg., twice daily for twenty-four days. The untoward reactions included drowsiness, nervousness, polydipsia and polyuria. Similar results were obtained with Pyribenzamine in 50 mg. doses four times daily for five days. In this patient, desensitization with subcutaneous histamine injections was without success.

Wide publicity has been given to the paper by Brewster,¹⁴⁷ who stated that the early administration of Benadryl, 50 mg. in adults and 10 to 25 mg. in children, at the onset of a cold completely aborted those of virus origin in 10 per cent of 100 patients, shortening the cold and giving marked relief to 95 per cent. The serous discharge from the mucous membrane of the upper respiratory tract is reported as being inhibited and subsequently also the cough reflex since postnasal drip was eliminated. The drug is said to abort the common fever blister when taken at the initial appearance of the wheal, and although there is no antipyretic effect, the soporific properties produce refreshing sleep. In a later paper, Brewster¹⁴⁸ used not only Benadryl but also Histadyl, and Thenylene (methapyrilene), Neo-Antergan and Pyribenzamine with which 572 patients were treated. In nineteen of twenty-one, all symptoms were aborted within the first hour after the onset of symptoms, and in forty-eight of fifty-five patients, within two hours. Of 156 patients who received treatment within six hours, 116, and of 234 patients who received treatment within twelve hours, 165, were also "cured." The parallel controls treated with codeine and papaverine showed less favorable results. From the author's personal experience, seven antihistaminic preparations taken at intervals of three hours for a common cold, typical in all manifestations, were completely without effect. On the other hand, Gordon¹⁴⁹ used not only Benadryl but also Pyribenzamine and Thephorin, reporting

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88 per cent of the patients relieved by 50 mg. doses every four to six hours, occasionally producing insomnia. A careful study of all of the papers on this subject shows that none are convincing, especially in the cases in which the antihistaminic agent was used with other substances known to give symptomatic relief. Time alone can prove the value of these drugs in virus or bacterial respiratory tract infections.

Benadryl, 50 to 200 mg. day, has been used in the lepromatous leprosy reaction by Moniz,¹⁵¹ some of six patients obtaining relief in five to eight hours after the start of an eight to ten days course. In two patients the drug was stopped after six days, there being no relapse in thirty to seventy days. Box¹⁵² confirmed this work in three patients treated with 50 mg. doses three times daily and for four additional patients, whose acute reactions were apparently precipitated by promin. In all cases, the courses of reaction seem to have been shortened and no new ulcers developed. The patients required no sedatives. In one patient the lesions improved and grew worse as Benadryl was repeatedly administered and withdrawn.

Of major interest is the paper by Stephens and Hollbrook,¹⁵² who in 1949 reported on eleven patients with collagen disease, four of whom were treated with Benadryl, 50 to 100 mg. daily. The seven untreated and one treated patient died within one to thirteen years after the onset of the disease. Autopsies confirmed the diagnosis. Three treated patients soon became asymptomatic. One who has continued treatment has remained free of symptoms for a year.

In 1945, Curtis and Owens¹⁵³ reported eleven of eighteen patients with acute or chronic urticaria who promptly relieved by oral Benadryl. Three patients were improved and four were not benefited. The effective dose was 50 mg. three times daily, with symptoms recurring when treatment ceased. Two patients complained of drowsiness and muscular soreness and one patient presented such severe vertigo, weakness and dizziness that the drug was discontinued. Two patients who took the drug for six months showed no toxic symptoms. At the same time, Shaffer et al¹⁵⁴ reported on eight patients, of whom seven received immediate relief from their chronic urticaria with 50 mg. of Benadryl four times daily. Relief occurred in thirty minutes for a patient with pruritus, in two days for a case of lichen urticatus and in two weeks for a patient with atopic eczema of thirty years' duration. In one patient with neurodermatitis, who was relieved by 50 mg. four times daily, the symptoms recurred when the drug was discontinued and thereafter the drug was ineffective in this patient, as it was in three others with neurodermatitis, dyshidrotic eczema and chronic lichen urticatus.

A report by O'Leary and Farber¹⁵⁵ showed that thirty-four of fifty patients with urticaria were completely relieved and twelve more were definitely improved on Benadryl, the pruritus disappearing in twenty to sixty minutes and the lesions in two to six hours. The duration of remission of twenty-five patients entirely relieved of chronic urticaria varied from one to three months. Those patients who showed intolerance were receiving 100 mg. three to four times daily. Toxic reactions described in order of decreasing frequency were drowsiness, dizziness, dilated pupils and dry mouth. In three patients the drug was discontinued because of severe dizziness, sensations of syncope and somnolence. A confirmatory report by Todd¹⁵⁶ showed forty-seven of fifty-two patients with acute or chronic urticaria, completely relieved, with partial relief in four, and one relieved of the wheals, but not the pruritus. Side reactions occurred in fewer than 25 per cent of the patients, who were treated both by the oral, intravenous and intramuscular routes.

Rosenberg and Blumenthal¹⁵⁷ used Benadryl intravenously and improved nineteen of twenty-one patients with urticaria with 30 mg. doses in 75 to 100 c.c. of saline, the injection taking seven to twelve minutes. The relief was noted as starting on the trunk and back and ending on the extremities, with the wheals blanching immediately and disappearing within one hour, the relief lasting from three to eight hours, with subsequent improvement by oral Benadryl. In three patients there were

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no recurrences. In two patients, whose urticaria followed the use of penicillin in oil and wax, the treatment was a complete failure. In three asthmatic patients, who had been unrelieved by various treatments, one was improved with intravenous Benadryl. Five patients suffering from jaundice with pruritus, gonorrheal arthritis, tabetic crises, unilateral headache and dysmenorrhea were not relieved. Eight patients demonstrated toxic reactions. In a second report, O'Leary and Farber¹⁵⁸ were able to describe the effects of Benadryl in 186 patients with various skin conditions. In acute urticaria, twenty of twenty-five were completely relieved after one to two days, with doses of 50 to 100 mg. daily orally every three to four hours. In chronic urticaria, forty-eight of seventy-five patients were relieved while taking the drug. Ten showed no benefit. Toxic reactions occurred in 31.3 per cent of the patients, in ten of whom the treatment had to be discontinued. In atopic dermatitis, eight of twenty-five patients were relieved of their pruritus, although in pruritus of other origin, the drug was ineffective. Of nine patients with scleroderma, seven were able to bend the fingers and make a fist two weeks after the treatment with 200 to 800 mg. per day. In only two was the benefit sustained.

That Benadryl ointment might be effective was shown by Philip,¹⁵⁹ who reported that in 84.4 per cent of the patients with neurodermatitis and 86.7 per cent of the patients with contact dermatitis, cure occurred with the use of an ointment containing 2 per cent Benadryl. Of the twenty-four different skin conditions, the average relief was 51.8 per cent described as complete and lasting, 21 per cent partial and 27 per cent little or no relief. No contraindications were noted. In this group, one patient with chilblains was relieved immediately upon application of the cream and had relief of symptoms throughout the cold months, although treatment was discontinued. The same cream, however, was used by Perry¹⁶⁰ in twenty-two patients suffering from various pruritic dermatoses, no significant relief being observed. The ointment was shown as not being absorbed sufficiently to decrease the diameter of the erythema in the size of the experimental histamine wheal in five patients following local application. In six of the patients whose itching was moderately relieved, in four equal relief was obtained by the application of the ointment alone. The contradictory nature of the reports on topical application with Benadryl is shown by the work of Orecklin.¹⁶¹ He used the 2 per cent ointment on 102 patients with generalized or local neurodermatitis. Seventy-seven were relieved; thirty-six of fifty-one patients with contact dermatitis and thirty-one of forty with nummular eczema, as well as twenty-eight of thirty-seven with pruritus ani vulvae or scroti, while twenty-four of thirty-eight with miscellaneous dermatoses were improved. In some instances, the ointment had to be applied every two to three hours, and even though relief of the pruritus occurred, many patients had exacerbations, some in either the same or in new locations four to six months after treatment. In this series, two per cent of the patients showed signs of sensitization or irritation following topical application. A single case of summer prurigo is reported by Woolhandler¹⁶² as being successfully treated by Benadryl.

It is obvious that Benadryl would be used in serum sickness and Peterson and Bishop¹⁶³ at a very early date described its success in both the early and late symptoms in ten children, aged two months to ten years, who suffered from meningitis, tetanus or diphtheria. A single dose of 50 to 100 mg. lasted six to twelve hours. The symptoms of serum sickness were completely abolished in two to three hours. The side reactions occurred more frequently when the drug was given as an elixir than as a powder. The authors feel that since the drug is probably effective in proportion to its concentration in the tissues, infants require two to three times as much per pound of body weight as do adults.

In 1946, Blank¹⁶⁴ described his experience with the intramuscular administration of Benadryl, 5 mg., relieving three patients with urticaria whose symptoms were subsequently controlled with oral doses of 50 mg. In one patient lethargy always fol-

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lowed the use of the drug. In addition, oral administration, 10 mg., relieved a child with edematosus fits of hives. One patient with angioneurotic edema suffered a headache, nausea, and lethargy after administration of Benadryl deriving no benefit from the drug. Therapy also failed in a patient with cold allergy. Patients with asthma did not respond. In Lockey's series¹⁴ of 171 patients, those with hay fever, acute and chronic urticaria and perennial vasomotor rhinitis, responded, but those with intrinsically asthmatic, incipient atopic dermatitis, erythema nodosum, sea or motion sickness and dysmenorrhea showed no response. Lockey stated that side effects were frequent and severe. Two patients with asthma, receiving 300 to 400 mg. daily for five days developed hallucinations and extreme drowsiness. One of these died suddenly. Frentholder¹⁵ had previously noted no definite therapeutic effect as seen in nineteen cases of bronchial asthma. An equal number of hay fever patients, who received 50 mg. three times daily, showed only two as clumping relief and two temporary improvement. The results, however, were coincident with a decreased pollen count. In sixteen of twenty-seven patients there was drowsiness, dizziness, faintness and gastrointestinal upsets. Three patients were completely intolerant to the Benadryl, although in ten out of eleven chronic cases of urticaria definite improvement, lasting two to twelve hours was seen within one hour after administration of 50 mg. In these same patients trial diets were given to those sensitive to foods, during temporary disappearance of the drug. Such symptoms as were reproduced by an aggravation, so they were controlled by the drug.

Burnett¹⁶ and Reichenberg¹⁷ used Benadryl to treat a number of unrelated conditions. Their report claims relief in twenty-four of twenty-nine patients with urticaria; fifteen of twenty-three with seasonal hay fever, one of twelve with bronchial asthma, twelve of sixteen with contact dermatitis, five of ten with functional dysmenorrhea, four of eleven with migraine; one of three with vasomotor coryza; two with spastic colon, and two with cough and mild asthmatic wheeze were also markedly relieved. Intravenous administration of Benadryl (20-50 mg /75-100 cc isotonic saline) suddenly controlled the pruritus of ten of eleven patients with urticaria and two with contact dermatitis, although two patients with bronchial asthma and one with tabetic crisis were not helped. Oral administration of Benadryl is believed useful in preventing severe transfusion reactions. The majority of the small group of patients with pruritus due to sunburn, jaundice and psoriasis were also reported as benefited. The inconsistency is shown by the report of Engelshier¹⁸ who found aggravation or no relief to occur in 127 of 193 patients, of whom only nine were definitely improved and the others, mildly so, although given either Benadryl or Pyribenzamine in more than adequate dosage.

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(To be continued in the May-June issue.)

COMPARATIVE STUDIES OF CERTAIN ANTIHISTAMINE DRUGS

(Continued from Page 233)

in many pharmacological respects. It is reasonable to assume that these drugs will give different results clinically. In some circles, there is an evident tendency to group all of the antihistamine drugs together. This is unwarranted.

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WHAT IS TO BE OUR BASIC PROFESSIONAL RELATIONSHIP?

(Continued from Page 239)

begins with symptoms and goes on to attitudes which have been denied to awareness, the perception of the relationship between these denied attitudes and her behavior, the reorganization of self to include these denied attitudes, and the consequent alteration of behavior.

CONCLUSION

I have tried to indicate the possibility that a very different relationship is called for in dealing with physiological and psychological problems. In handling organic problems, the relationship is most effective if responsibility, learning, and accurate, objective evaluation are lodged primarily in the expert. In dealing with psychological conflict, our work would indicate that the responsibility, the self-initiated learning, and accurate perception and evaluation of inner experience must be lodged with the client. The expert has an effective relationship with the individual when he is able to create the atmosphere which facilitates such processes in the client.

The worker in psychosomatic medicine is at the heart of the problem created by the need for these two different types of relationships. How can he deal effectively with both elements—those organic aspects over which the patient can have no conscious control, and those psychological elements which can potentially come into awareness and thus under conscious control? I cannot give you the answer, but I think the first step in finding the answer is to face the basic contradiction in relationships which I have tried to pose.

University of Chicago

News Items

SOUTHWEST ALLERGY FORUM

A very well attended and enthusiastic meeting marked with the usual Southern cordial hospitality was held at the Hotel Peabody in Memphis April 2-4. There were five round tables covering important subjects in allergy. President John H. Mitchell of the American College of Allergists and President Theodore F. Squier of the American Academy of Allergists gave luncheon addresses. Social activities featured a cocktail party followed by a banquet the first evening of the session.

NEW ARGENTINE ORGANIZATION

A new allergy organization has been formed in Argentina known as the Asociación de Alergia e Inmunología. The address is Cangallo 1435, Buenos Aires. The executive committee is as follows: President, Dr. Benigno R. Garat; Vice-president, Dr. José A. Bózzola; Secretary, Dr. Carlos R. Landa; Treasurer, Dr. Osvaldo Rossi Richeri; Chief Editor, Dr. Rubén A. Binaghi. This is not to be confused with the older allergy society in Argentina known as Sociedad Argentina de Alergia, which is an official member of the International Association of Allergists.

It is earnestly hoped that there will be cordial relations between the two national societies, which is so essential for the best interests of allergy not only in the Argentine but in promoting international relationship with allergy societies of other countries.

PSYCHOTHERAPY COURSE FOR ALLERGISTS

Your attention is called again to the Psychotherapy Course for Allergists to be given by Dr. Sandor Rado, Clinical Professor of Psychiatry and Director of the Psychoanalytic Clinic for Training and Research, Columbia University, beginning Monday, November 6, and ending Friday, November 10, 1950. The course is being given with the co-operation of the American College of Allergists. Other members of the staff of the Psychoanalytic Clinic will also participate in the program of the course. Lectures will be held from 9:00 a.m. to 12:30 p.m. and from 2:00 p.m. to 5:00 p.m. daily, and it may be that evening round-table discussions will be presented also.

The registration is limited, but there are some vacancies left. The registration fee is \$100. Write to Dr. Harold A. Abramson, 133 East 58th Street, New York, New York, for details. This is a privileged opportunity for you to increase your understanding of the relation of psychodynamics with basic medical sciences. You will have the advantage over other allergists who do not appreciate the importance of psychosomatic allergy at the present time. The course will also familiarize you with the psychological aspects of the patient-physician relations and with the techniques of the minor psychotherapy of the allergic patient.

HUNGARIAN SECTION OF ALLERGISTS

The section of Hungarian allergists held its symposium entitled "Liver and Allergy," on October 20, 1949, at Budapest. Pathologists particularly interested in liver diseases participated in the proceedings. Following the chairman's introduction, Doctor Farkas presented the histological changes, interpreted as allergic, in asthma, eclampsia, and endophlebitis. Doctor Farkas agreed that allergic factors play an important role besides the icterogenic virus in the etiology of infective hepatitis. The discussants were Drs. Filipp, Vegh, Kobulniczky, Rajka, Fornet and Hajos.

NEWS ITEMS

Drs. M. K. Hajos, O. Riedl and G. Szecsey spoke on the hepatic reactions in allergic diseases, indicating that 30 per cent of allergic patients, mainly those with asthma, showed abnormal liver function tests. They emphasized the importance of introducing more exact methods for investigation of liver functions. In the discussion, Doctor Radnoti proposed the determination of differential-nitrogen as an important diagnostic test. Doctors Filipp, Kelenhegyi and Jona discussed in their lecture the organic liver shock, and found that hepatic lesions resemble the Masugi kidney. Animal experiments revealed abnormal liver function tests along with histopathological changes. On the day following, the section on allergy held its regular session.

Dr. L. Mosonyi described allergic investigations in the Soviet Union. Doctors Kemeny and Filipp discussed "Hypophysis and Anaphylaxy," and stated that hypophysectomy rendered animals susceptible to anaphylaxis, and that anterior pituitary lobe extracts inhibited the shock. Doctor Hajos mentioned his own experiments concerning the relation of endocrine function and anaphylaxis.

Doctor Hajos gave an address on "Environmental Influence in the Etiology of Allergic Diseases" and enumerated exogenous factors and social problems influencing allergic diseases. Following this there was a discussion by Doctors Filipp, Csefko, Végh, Kerdo, Fornet and Rajka. Dr. E. Feher discussed micogenic allergy. Doctor Mosonyi presented "Antibiotics and Allergy." Doctor Rudas remarked on the successful desensitization to penicillin and streptomycin.

PENNSYLVANIA ALLERGY ASSOCIATION

The program of the Pennsylvania Allergy Association which will meet at the Bedford Springs Hotel on May 11, 1950, is as follows:

Wednesday, May 10, 1950

9:00 P.M. Parlor "A"—Board of Regents Meeting

Thursday, May 11, 1950

9:00 A.M. Parlor "A"—Business Meeting for Members

12:30 P.M. Parlor "A"—Luncheon for Members and Guests

7:30 P.M. Parlor "A"—Banquet for Members and Guests

Chairman of Scientific Session—Morning, H. A. SLESINGER, M.D., Windber. Afternoon, BEN HAMNER, M.D., Williamsport.

Scientific Exhibits

Anthrocilicosis and Pediatric Allergy—H. A. SLESINGER, M.D., Windber

Inhalation Therapy and Botanical Slides—STEPHEN LOCKEY, M.D., Lancaster

The Problem of Bronchial Asthma—WILFRED Langley, M.D., Sayre

Pictures of Molds—JOSEPH PIEKARSKI, M.D., Wilkes-Barre

Morning Session

9:50 A.M. "Welcome"—President of Bedford Medical Society

9:55 A.M. "Welcome"—L. R. ALTEMUS, M.D., 11th District Councilor

10:00 A.M. "Explosive Reaction in Dermatologic Allergy"—JOSEPH RICCHUITI, M.D., Pottsville

Discussion opened by WILFRED Langley, M.D., Sayre

10:30 A.M. "The Botany of Allergy"—EDWARD CLAUS, M.D., University of Pittsburgh, Pittsburgh

Discussion opened by RUTH WILSON, M.D., Beaver

11:30 A.M. "Gastro-intestinal Manifestations of Allergy During Childbirth"—JOSEPH FRIES, M.D., Brooklyn, New York

Discussion opened by LUTHER KING, M.D., Meadville.

NEWS ITEMS

- 12:00 P.M. "X-Ray and Its Importance in the Diagnosis and Treatment of Allergic Disorders"—WALTER WERLEY, M.D., Reading
Discussion opened by NICHOLAS SARGENT, M.D., Falls Creek
12:30 P.M. Intermission

Afternoon Session

- 2:00 P.M. "Drugs in Allergic Therapy"—STEPHEN LOCKEY, M.D., Lancaster
Discussion opened by JAMES MANSMANN, M.D., Pittsburgh

- 3:00 to 5:00 P.M.—"The Present Status of Bacterial Allergy"
"Ask the Experts"

A question and answer quiz with a minimum of prepared statements.
Please participate by presenting your problems

Panel Members

- RICHARD A. KERN, M.D.—Professor of Medicine, Temple University, Philadelphia
"The Present Status of Bacterial Allergy" (10 minutes)
- RUSSELL C. GROVE, M.D.—Chief Otologist, Allergy Clinic Roosevelt Hospital, New York City
"Bacterial Allergy in Otorhinolaryngology" (10 minutes)
- JOHN E. GREGORY, M.D.—Head, Division of Pathology, Hahnemann Medical College, Philadelphia
"The Role of Allergy in Rheumatic Fever" (10 minutes)
- ARCHIBALD R. JUNN, M.D.—Superintendent, Pennsylvania State Sanatorium of Tuberculosis No. 3, Hamburg, Pennsylvania (10 minutes)

Moderator

- PAUL C. CRAIG, M.D.—Secretary for Instruction, Pennsylvania Academy of Ophthalmology and Otolaryngology

RALPH M. MULLIGAN, M.D.
Secretary-Treasurer

CORRECTION

In the paper entitled "Cottonseed Protein vs. Cottonseed Oil Sensitivity" published in the January-February number of the *ANNALS*, the following corrections should be noted:

The third footnote on Page 4, Table II, should read "Ratio of specified threshold to ingestion threshold."

On Page 5, Paragraph 5, line 6 should read: "was relatively great, from one-sixth to one-three hundredth the ingestion doses being required to ex-."

HYPO-ALLERGIC PENICILLIN

(Continued from Page 201)

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BOOK REVIEWS

MEDICAL ETYMOLOGY. The History and Derivation of Medical Terms for Students of Medicine, Dentistry, and Nursing. By O. H. Perry Pepper, M.D., Professor of Medicine, University of Pennsylvania. 263 pages. Price \$5.50. Philadelphia: W. B. Saunders Company, 1949.

This handbook is the answer to a rapidly new and bewildering medical, dental, and nursing terminology. Medical schools in general do not have an adequate course in scientific terminology. The book gets away from the style of a dictionary, since it is concerned more with the origin or derivation of words than with the meaning. Its less than 4,000 terms represent almost all of the roots the student will encounter, so that he will be released from slavish dependence on a medical dictionary with its 50,000 or so words. The data in the book are presented in a manner to be available and helpful to the student.

There are four parts, the first of which consists of an introduction giving background of medical terminology, prefixes, suffixes, compounds and transliteration, eponyms, and onomatopoeitic words.

The second part deals with preclinical subjects, the third with clinical subjects, and the fourth with dentistry. There is a comprehensive index which serves also as a ready reference for the spelling or the difficult medical terminology commonly used. All authors could use this book to great advantage in improving their writing.

PSYCHIATRY IN GENERAL PRACTICE. By Melvin W. Thorner, M.D., D.Sc., Assistant Professor of Neurology, The Graduate School of Medicine, University of Pennsylvania, with a foreword by C. Charles Burlingame. 659 pages. \$8.00. Philadelphia: W. B. Saunders Company, 1949.

The author's purpose is aptly expressed when he states, "This volume is an attempt to lift psychiatry out of the realm of *terra incognita* for those whose primary efforts are spent in other fields."

The book is characterized by presenting psychological medicine that is very interesting from the professional point of view, yet avoiding the sensational. Such a book obviously must present case histories which represent actual experience with patients. The author succeeds admirably in doing this. The book is a departure from the many texts on the subject which do not recognize the importance of the association between psychiatrists and men in other branches of medicine. For the internists and general practitioners who wish to apply psychiatry in their practice, it is most valuable. It is written in understandable language for those who see and treat patients rather than for the academic psychiatrist or the psychoanalyst. The patients' problems are presented first, followed by logical generalizations and deductions.

The volume is well organized, and the material is arranged roughly in three sections. Each section has a list of excellent selected references. There is an appendix of classification of mental disorders, as well as one of committal procedures.

The book is well bound, the print is very clear and readable, and the case reports are in italics.

1950 CURRENT THERAPY. Latest Approved Methods of Treatment for the Practicing Physician. Edited by Howard F. Conn, M.D., with Twelve Consulting Editors and 269 Contributors. 736 pages and numerous tables. Price \$10.00. Philadelphia and London: W. B. Saunders Company, 1950.

This is the second annual volume of a book which is different both in concept and in content from any other book of its kind. There are sixty-three pages of additional material this year, and it affords a ready desk reference of detailed, authoritative articles on the very latest treatments for every disease and condition encountered by

BOOK REVIEWS

the practicing physician or the specialist, whether the disease occurs frequently or rarely. Every effort is made to present the best treatment available today for that particular disease, according to the Board of Consultants, who selected each contributor as an authority with practically the most effective treatment for any disease in question. Experimental or highly controversial methods are omitted, and the volume does not represent excerpts from the literature but the actual experience of the contributors.

Each article was written especially for this text and represents the work and report of a foremost authority describing the method he is using in treating this particular disease at the present time.

The section on allergy comprises pages 407-441, including all of the diseases definitely known to be due to allergy.

The book is very durably and attractively bound, and the two-column style facilitates reading. It is arranged in fourteen convenient sections. Each section is prefaced by a "Contents" page listing alphabetically where each disease may be found in the book. The text has had a phenomenal distribution since its appearance last year, and any practicing physician or specialist in any field of medicine will find readily at hand a concise, authoritative treatment of diseases in general.

A STUDY OF THE ANTIGENICITY OF ATOPIC REAGIN

(Continued from Page 222)

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Abort the mild asthma attack
anywhere,
any time—with

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1. Gay, L. N., and Long, J. W.: Clinical Evaluation of Isopropylepinephrine in Management of Bronchial Asthma. Council on Pharmacy and Chemistry, Report to the Council, J.A.M.A., 139:452, Feb. 12, 1949.

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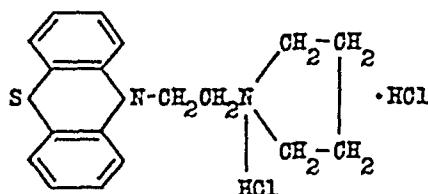
Number 3

PYRROLAZOTE. A CLINICAL EVALUATION IN ALLERGIC STATES

HENRY D. OGDEN, M.D., F.A.C.A., VINCENT J. DERBES, M.D., F.A.C.A., and
LOUIS CULLICK, M.D.

New Orleans, Louisiana

We are reporting clinical experiences with a new antihistaminic agent, Beta-pyrrolidineethyl-phenothiazine hydrochloride (Pyrrolazote).*



This drug was initially made available in 50 mg. tablets, and the dosage used was varied in accordance with the response of the patient. The usual dose was one tablet twice or three times daily, but larger or smaller amounts were sometimes used.

In Section I of this report there is a record of experiences with these 50 mg. tablets of Pyrrolazote in the L.S.U. out-patient clinics of Charity Hospital. In these cases Pyrrolazote was compared with placebo medication (L.C.). In Section II of this study placebos were not employed. An elixir containing 75 mg. per ounce was given to children. The data obtained for this second section were derived from the office records of two of us (H.D.O. and V.J.D.).

SECTION I—METHOD

Forty-six patients with asthma, hay fever, combined asthma and hay fever, and two cases of urticaria were utilized. Patients were selected at random, no attempt being made to differentiate the type of respiratory allergy, i.e., intrinsic or extrinsic asthma, or the type of nasal allergy.

Presented at the Fifth Annual Meeting of the American College of Allergists, April 14-17, 1949, Chicago, Illinois.

*Kindly supplied by the Upjohn Company, Kalamazoo, Michigan.

Patients were alternated from week to week on Pyrrolazote and a placebo for varying periods of fifteen to twenty weeks. Each patient at each clinic visit was given a one-week supply of Pyrrolazote and a mimeographed form to fill out. On this form the patient was to give the time of onset of attacks, severity of symptoms, duration of attacks, the number of tablets taken, and the frequency with which the tablets were taken. These patients were also to record any side reactions that were noted, and to facilitate this a list of symptoms experienced with other antihistaminics was printed on the form. At the return visit the following week, the forms would be evaluated, the Pyrrolazote collected, and a week's supply of placebo issued with a similar form. Patients took Pyrrolazote and placebo on alternate weeks during the study. It should be pointed out that asthma was present in a large percentage of these patients (61 per cent of forty-six). This was due to the fact that there was no selection of patients, and asthmatics are in a large majority in the out-patient allergy service of Charity Hospital. That poor results are obtained with antihistaminics in asthma has long been recognized.

RESULTS

Results were evaluated according to the number of hours of mild, moderate, and severe symptoms while on the drug and on the placebo. Dr. Huldah Bancroft, Professor of Biostatistics, Tulane University School of Medicine, tested the results (Table I).

TABLE I. AVERAGE HOURS OF SYMPTOMS PER WEEK PER PATIENT

	Placebo	Drug	P*
Mild symptoms	4.40 hours	4.33 hours	—
Moderate symptoms	4.09 hours	2.75 hours	0.23
Severe symptoms	10.55 hours	5.08 hours	<0.0001
Moderate and Severe symptoms	14.64 hours	7.83 hours	0.0001
Total symptoms	19.04 hours	12.17 hours	<0.0001

*P = probability that a difference as great as or greater than this would occur by chance. This probability was determined from the formula:

$$C.R. = \frac{\text{Mean}_1 - \text{Mean}_2}{\sqrt{\frac{S.E._1^2}{2} + \frac{S.E._2^2}{2}} - 2r S.E._1 S.E._2}$$

$$\sqrt{\frac{S.E._1^2}{2} + \frac{S.E._2^2}{2}} - 2r S.E._1 S.E._2$$

There was no significant difference between mild and moderate symptoms while on the drug and while on the placebo, but a significant difference in severe symptoms is noted. There were 10.55 hours of severe symptoms per patient per week while on the placebo in comparison with 5.08 hours of severe symptoms per patient per week while on the Pyrrolazote. As great a difference or a greater difference than this would be expected to occur by chance less than 1 time in 10,000. This reduction in the hours of severe symptoms is considered significant. The difference in the total symptoms (mild, moderate, and severe) is also significant. There was an average of 19.04 hours per patient per week while on placebo as compared with 12.17 hours while on Pyrrolazote.

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It is felt that the degree of symptoms must be taken into consideration, as it would be faulty to compare hours of severe symptoms with hours of mild symptoms. The severity of symptoms were evaluated by the patients themselves; this, of course, is a subjective evaluation. However, in this study the errors of subjective interpretation were obviously neutralized since both groups were crossed over and because the total hours of all degrees of symptomatology were computed for both groups. Patients were not informed that they were taking placebos.

The results were also evaluated according to statements made by individual patients. These are classified in Table II according to type of case.

TABLE II. RESULTS REPORTED BY PATIENTS

	Pyrrolazote				Placebo			
	Good	Mod.	Poor	None	Good	Mod.	Poor	None
Hay fever and asthma	13	2	2	3	8	2	4	6
Hay fever	13	2	2	0	10	1	3	3
Asthma	3	1	1	2	2	0	2	3
Urticaria	1	1	0	0	0	0	0	2

In the group of combined hay fever and asthma, there was no breakdown in the two syndromes, and some of the five patients with poor or no relief while on the drug might have had relief from nasal symptoms even though the asthma was not benefited.

It is noted that there are a large number of patients who received benefit while on the placebo. However, we feel that in any study of this type this is not unusual. In many of these patients these good results could be attributed to various factors such as excessive co-operation, neurosis, spontaneous disappearance of symptoms which would have subsided without any medication, et cetera. * * *

TABLE III. SIDE REACTIONS

	On Pyrrolazote	On Placebo
Mild drowsiness	30	21
Severe drowsiness	1	1
Nausea	13	9
Severe nausea	0	1
Vomiting	6	4
Headache	18	12
Palpitation	1	0
None	8	18

These findings indicate that when patients are warned of possible side reactions and particularly if they have experienced them on the drug, they are quite apt to complain when on the placebo. Possibly certain of the reported side reactions to various antihistaminics are attributable to warnings given to the patient simultaneously with the medication.

**Since this article was submitted for publication, Stewart Wolf in his article, "Effects of Suggestion and Conditioning on the Action of Chemical Agents in Human Subjects," (*J. Clin. Invest.*, 29:100-110, January, 1950) has reported that "placebo effects" which modify the pharmacologic action of drugs or endow inert agents with potency are not imaginary, but may be associated with measurable changes at the end organs. These effects are at times more potent than the pharmacologic action customarily attributed to the agent.

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SECTION II

In this part of the study we are evaluating our observations on the drug in 130 patients. Some patients had more than one symptom; therefore the total number of symptoms is larger than the group of patients. In this group the patients were merely given Pyrrolazote tablets and asked to report the results. This is the type of study that has been followed by most clinical investigators with other antihistaminics. We have used it in the conditions listed in Table IV.

TABLE IV

	Good	Moderate	Poor	None
Hay fever	45	6	3	7
Chronic allergic rhinitis	35	2	1	5
Allergic tracheobronchitis	5	0	0	0
Bronchial asthma	6	0	2	5
Urticaria	6	1	0	0
Headache	3	1	0	2
Pruritus ani	3	0	0	0

TABLE V. SIDE REACTIONS

Stimulation	1	Weakness	1
Drowsiness	39	Dizziness	1
Hypnosis	7	Abdominal cramps	1
Nausea	14	None	71

However, since this study was begun, we have commenced using another Pyrrolazote preparation. These are Pyrrolazote-coated delayed action tablets containing 25 mg. of Pyrrolazote base (present as the hydrochloride) in the outer coat, available for immediate absorption. Twenty-five mg. is present in an inner, Ileosol-coated tablet. It is felt that such a tablet will serve to prolong the effectiveness of a single dose of the drug, possibly enough to carry through the sleeping hours of the patient. It had previously been observed that many patients would do well on half of the 50 mg. tablet and that the incidence of side reactions was thereby greatly reduced.

TABLE VI. PYRROLAZOTE—TWO STAGE (32 PATIENTS)

	Good	Mod.	Poor	None
Hay fever	3	1	0	1
Chronic allergic rhinitis	11	3	0	1
Urticaria	3	1	0	0
Bronchial asthma	1	0	0	0
Allergic tracheobronchitis	1	0	0	0
Headache	1	0	0	0
Rhinitis medicamentosa	0	0	0	1
Atopic eczema (relief of itching)	1	0	1	0
Pruritus	3	0	0	0
Localized neurodermatitis	0	0	0	1

Two of these patients had more than one symptom. Slight drowsiness appeared in two of them, and some nausea in three.

In addition to the two groups reported above, Pyrrolazote tablets (usually the two-stage type) were later used in an additional twenty-six office patients (H.O.). Six patients had more than one symptom. The results reported were as follows:

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TABLE VII. PYRROLAZOTE—MIXED OFFICE GROUP

	Flood	Moderate	None
Urticaria	5	0	1
Chronic allergic rhinitis.....	13	2	3
Asthma	1	0	1
Contact dermatitis	1	0	0
Conjunctivitis	0	0	2
Hay fever	2	0	0
Vomiting	1	0	0

Three patients reported slight drowsiness and one had marked drowsiness. One patient complained of insomnia, while another had dizziness and headache. It is felt that the percentage of side reactions is greatly lessened when the two-stage preparation is used. No attempt is made in the paper to combine these three groups, because the plain and two-stage tablets have a different period of action.

In scratch tests sites of three patients that were treated with 5 per cent Pyrrolazote solution (sterile), definite inhibition of histamine flares were observed. In another patient inhibition of a ragweed skin reaction was obtained.

CONCLUSIONS

1. Pyrrolazote is a potent antihistaminic which compares favorably with other similar preparations.
2. Placebo controls show that there is a significant difference in amount of severe and total symptoms while on the drug.
3. A large percentage of patients taking placebo tablets complained of side reactions. Therefore, the element of suggestion must be considered in evaluating such reactions to any antihistaminic.
4. The new two-stage tablet appears to be effective. Side reactions were mild and infrequent.

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CORRECTION

In the January-February issue of ANNALS OF ALLERGY, "Allergic Toxemia and Fatigue" by Albert H. Rowe, M.D., F.A.C.A., there appeared two references to Tomas Mariante. The first is on page 72, line 12; the second on page 79, reference 2. The author of the work cited, *Toxemia Alergica*, is Nino Marsiaj, M.D., F.A.C.A., Brazil. Dr. Mariante was also a contributor to the book, but the article on allergic toxemia was written by Dr. Marsiaj.

SOME ASPECTS OF ALLERGY OF THE EYE

VERA B. WALKER, M.Sc., Ph.D., M.R.C.S., L.R.C.P.

Oxford, England

THE history of this subject is well known. The monograph "Die Anaphylaxie in der Augenheilkunde" of von Szily,¹⁷ published in Stuttgart in 1914, coupled with that excellent one nearly twenty years later by Professor A. C. Woods,²⁰ provides an historical background for the present paper.

The first important study of allergic conditions of the eye in England was published by Blackley² of Manchester: "Experimental Researches on the Cause and Nature of Catarrhus aestivus." It is not generally known that Blackley published a second edition in 1880, adding two more chapters devoted to treatment. Blackley's graphic description of the conjunctival test with locally grown pollens is well worth recalling:

Para. 136. "A decoction of the pollen of Gladiolus was made by boiling a portion of this with one hundred times its weight of distilled water. One drop of this liquid was placed in contact with the conjunctiva of the right eye. The effect was almost instantaneous. The first sensation was that of intense burning and smarting, coupled with a feeling such as might be imagined to be caused by fine sand being blown into the eye. The photophobia was so severe that for some minutes the eye could not be opened for more than a single second at a time. In about thirty seconds the capillary vessels of the conjunctiva were seen to be greatly distended. With the aid of a lens the larger vessels of the conjunctiva could be seen to be raised above the surface. Movement of the eyeball gave great pain, just as is felt when dust has been blown into the eye. In six minutes the conjunctiva had become quite edematous, but showed its closer attachment as far as the outer margin of the cornea. The edema increased until very severe chemosis was set up. The eyelids also became much swollen. In two hours after the fluid had been applied the smarting and burning had much abated, and the congestion of the conjunctival vessels had considerably lessened, but the chemosis remained and was even more marked than it had been an hour before. There was a moderately copious discharge of fluid from the eye and also some little from the nostril. In six hours the eye still felt uneasy, but there was very little pain on moving the eyeball, although the vessels of the conjunctiva were still injected. The chemosis still remained as severe as before. In eighteen hours there was scarcely any congestion of the vessels remaining, but the chemosis was still very distinct. In thirty-two hours all traces of the derangement had disappeared. During the course of this experiment no effect was produced on the sclerotic coat of the eyeball, nor yet, so far as could be seen or felt, on the deeper structures. The action seemed to expend itself upon the conjunctiva and upon the cellular tissue of the eyelids."

A generation later this conjunctival test was extended and used by Noon and Freeman.⁴ Noon¹⁰ was a great observer. He used as little as five to seven grains of pollen for "active immunity" treatment, and knew that if he used larger doses, he did harm rather than good. In recent times this has been replaced by other tests, less embarrassing, and perhaps less dangerous for the patient.

Presented at the Sixth Annual Meeting of the American College of Allergists, St. Louis, Missouri, January 17, 1950.

This study is based on 17,150 cases observed over a period of ten years.

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TABLE I. EYE HOSPITAL OUTPATIENTS

Presenting Pathologic Condition	Approximate per cent of Cases Proved to be of Allergic Origin 1941-6	Approximate per cent of Cases Proved to be of Allergic Origin 1941-9
Angioneurotic edema	70	70
Blepharitis	10+	15
Conjunctivitis	40+	43
Keratitis	10	10
Keratitis rosacea	70	78
Episcleritis	7.5	8
Iritis	3	8
Iridocyclitis	2.5	11
Glaucoma	5	5
Acute congestive glaucoma	—	15
Retinal hemorrhage or detach	1	1
Choroiditis	3	3
Cataract	0.2	0.4
Retro-bulbar neuritis	—	45
Migraine	54	63

In opening a discussion on "Allergy in Ophthalmology" at the Royal Society of Medicine in 1947, Mr. Gayer Morgan⁵ (senior ophthalmic surgeon at Guy's Hospital) reminded us that almost every disease of the eye had been reported as allergic in origin in some particular case. The truth of this statement is all too obvious from the copious literature on the subject, but how much more widely applicable if we delete the word "disease" and replace it by "condition." To me an allergic condition is acute in onset, and if recognized and treated at once will clear up quickly, often within a few minutes or hours, leaving no permanent damage to the tissues involved; but it must be recognized that once a tissue has remained in an abnormal physiological condition for some time, as in recurrent keratitis or iridocyclitis, there may be secondary changes due perhaps to pressure of edema, to inflammation, or to secondary infection, which must be healed by routine treatment and may leave permanent scarring.

To explain why one organ, be it eye, ear, chest or skin, is selected as the "shock tissue" to carry the full responsibility of an allergic reaction, takes us into the realm of metaphysics: and indeed I hope to demonstrate that not the eye as a whole but one tissue only (perhaps conjunctiva, cornea, iris, lens, et cetera) is, as a rule, concerned in the manifestation of allergy in any given patient. Why any one tissue is selected for such abuse we do not know. Many readers may believe, and perhaps rightly, that some previous injury, either traumatic or developmental, is necessary. This idea seems to help in the explanation of unilateral allergic conditions in one of two symmetrical organs.

Depending on which tissue is sensitized to the offending allergen, we may see angioneurotic edema, blepharitis, conjunctivitis, keratitis, episcleritis, iritis, iridocyclitis, glaucoma, retinal hemorrhage or detachment, chorioditis, cataract, retro-bulbar neuritis, or migraine.

From Table I it can be seen that some of these conditions are frequently allergic and some only occasionally so. The first column of figures (1941-6) was published in the *British Journal of Ophthalmology* in 1948 (Walker¹⁸). Three more years' investigations have been added, and the results summarized in the second column are complete up to 1949. Several points deserve comment:

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Angioneurotic Edema.—An allergic cause can be found for 70 per cent of these edemas, but if we included only those patients who, during the attack, have some other associated manifestations of allergy such as conjunctivitis, edema of cornea, or migraine, this figure increases considerably, and practically 100 per cent are proved to be allergic in origin. Presumably those of psychosomatic and hormonal origin would thus be eliminated from the series.

Acute Iritis.—Acute iritis, with or without involvement of the ciliary body, is occasionally presented to the allergist for investigation, especially when the patient is a chronic asthmatic. The psychological trauma due to sudden acute pain may precipitate an attack of asthma, and so help in the diagnosis. When one remembers that the iris is a "diaphragm of blood vessels and unstriped muscle fibres held together by a very loose spongy stroma" (Parsons and Duke-Elder,¹¹) one cannot fail to recognize an almost ideal setting for an acute anaphylactoid reaction. While the routine treatment of atropine and heat must be applied in all acute iritis cases, if the attack is possibly of allergic origin 1 c.c. of epinephrine 1/1,000 injected subcutaneously, slowly, will relieve the pain in a few minutes instead of in hours or days. Such acute iritis cases may be due to foods, inhalants, drugs or toxins (including tuberculin), and should have the advantage of a full range of allergy tests between, not during, acute attacks.

Iridocyclitis.—The increase from 2.5 to 11 per cent (Table I) is partly explained by inclusion of some post-accident cases of acute cyclitis. The trauma of the accident may act as a trigger for some allergic response to airborne allergens or drugs; or if the lens capsule is torn in any accident, the surrounding tissues become sensitized by the escaping material. The stage is now set for an allergic response in this, and perhaps also in the other eye, if any operative procedure is necessary during the next few days or weeks. A typical example is described in Case 1.

Case 1

Male, aged 38

1st day.....	Perforating injury of left eye with lens puncture. No F.B. found.
10th day.....	Routine treatment in hospital, including penicillin locally.
11th day.....	Reported at Outpatients. No pain but worried by loss of vision. Curette evacuation of swollen lens (not whole) and A.C. washout.
12th day.....	Acute cyclitis of L. eye and some discomfort in R.
a.m.	Severe cyclitis in L. eye. Slight iridocyclitis in R. (Sympathetic ophthalmitis).
12th day.....	Routine allergy tests. All inhalants, pollens, foods and drugs negative.
p.m.	Uveal pigment —ve Lens protein +++ (intradermal)
	Desensitization to lens protein by graded intramuscular injections 3-hourly for 3 days.
15th day.....	R.E. normal in appearance and vision.
17th day.....	L.E. still slightly injected but all discomfort gone. Vision 20/120. Further washout of A.C.
23rd day.....	Lens protein disturbed without any flare-up. Vision R.E. 20/20 Discharged from hospital.
53rd day.....	Vision R.E. 20/20 L.E. 20/80

Also included in the 1949 list, but not in the 1946 one, are those cases of chronic recurrent iridocyclitis of which it had been agreed by the ophthalmologists and pathologists that the inflammation was of "virus origin."

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TABLE II. ACUTE CONGESTIVE GLAUCOMA

Case	Allergen Found	Treatment		Time Before Tension Normal
		General	Local	
Male (44)	Pollen	Epinephrine Adrenaline 1 c.c.	Eserine	6 hours
Female (55)	Pollen	Epinephrine Adrenaline 2 f.c.	Pilocarpine	3 hours
Female (23)	*Streptococcal Infection	Antisan	Pilocarpine	20 hours
Female (65)	Tomatose	Benzidyl	nil	4 hours
Male (55)	Fluor. Cysticercus	Benzidyl	Eserine	16 hours

*Complicated by fungal infection.

Known to have "asth." and mix all his life.

So far, although we have frequently used bacterial allergens prepared from streptococcal, staphylococcal or tubercle protein, no attempt has been made in our hospital to prepare a virus allergen. Some persons will champion the view that recurrent clinical manifestations of virus disease, occurring after an incubation period, are due to propagation of the virus itself, rather than to a development of hypersensitivity, and so to attainment of a state of clinical allergy. All viruses are not self-limiting, so in the absence of any satisfactory drug treatment for the viruses themselves we find that a state of stagnant depression of both doctor and patient rapidly develops, becoming more intense with each recurrence, as the threat of ultimate blindness looms on the horizon. In an attempt to help in what is perhaps a losing fight, treatment of chronic iridocyclitis by nonspecific anti-allergic methods is being explored. Results are not yet ready for publication, but a pilot survey indicates that the use of full doses of antihistamines by mouth during an acute exacerbation, followed immediately by desensitization with histamine, overcomes the tendency to recurrences, and so delays any deterioration of vision, perhaps for years. The tentative suggestion is made that the tendency to develop a state of clinical allergy has been reversed. So in Table I the figure of 11 per cent includes not those iridocyclitis cases, reporting once and once only, caused by acute infection or trauma, but those who have come with a first or subsequent recurrence, and after receiving what may be loosely termed "reduction of sensitivity" treatment, have avoided further recurrence for at least three years.

Acute Congestive Glaucoma.—It is often recorded in hospital notes that the pain of acute glaucoma was intense enough to cause vomiting; further questioning of the patient will sometimes elicit the statement that the biliousness started before the pain, and indeed that there had been previous attacks of vomiting accompanied by some transient dimness of vision with or without neuralgia in the region of the fifth nerve. This, together with the edema of lids and conjunctiva and the venous dilatation causing dusky red coloration of conjunctivae, the cloudiness and lack of sensitivity to

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TABLE III. KERATITIS ROSACEA I

100 Patients (1940-1947)

	Presenting Symptom	
Group I	Face lesions only	23
Group II	Face lesions + palpebral conjunctivitis	18
Group III	Face lesions + palpebral and bulbar conjunctivitis	28
Group IV	Face lesions + conjunctivitis and slight keratitis	10
Group V	Face lesions + keratitis with severe scarring	21
		100
All of these, if untreated, are potentially in Group V.		

TABLE IV. KERATITIS ROSACEA II

Group A. (Table III)		
Allergic cause for both face and corneal lesion found by skin tests, exclusion diets, contact history etc.....		78
Group B.		
No proof of allergic origin of lesion.....		22
		100

touch of the cornea, and the discoloured iris, suggests an acute allergic state, and may be proved to be so in at least 15 per cent of cases. Typical examples are shown in Table II.

The work of Kirwan⁸ should be recalled. He investigated the glaucoma associated with epidemic dropsy in India and reported that the essential feature is a capillary dilatation and increased permeability throughout the uveal tract due to the action of a histamine-like substance present in the aqueous and vitreous, which is also responsible for the general tissue edema in this epidemic dropsy. Though the tension was often raised to near 100 mm. Hg (Schiötz), local treatment was valueless, but the eye condition began to improve when general treatment was instigated. This consisted of eliminating rice from the diet and washing out the alimentary tract. Allergists will appreciate the probability that not the rice, but rather some mold on the rice may have been the responsible toxin.

[Pathology: Ciliary body showed vascular dilatation and edema of tissues without abnormality of the epithelium. Enormous vasodilatation in the choroid. Filtration angle shows complete absence of abnormality.]

Keratitis.—Although only 10 per cent of all cases of keratitis seem to come into the allergic group, a very much greater figure is obtained in a sub-group with those where the corneal lesion is associated with rosacea. Rosacea is the presenting symptom of an abnormality of the superficial epithelium of the face of adults between the ages of twenty and fifty years. An attack may last a few weeks or months, but tends to clear up only to recur again at increasingly frequent intervals, eventually being accompanied by ocular manifestations, varying in degree from a mild conjunctivitis through all the stages of blepharo-, tarsal- and bulbar-conjunctivitis to keratitis, and eventual visual incapacity.

[Pathology of skin lesions of rosacea (Roxburgh):¹⁴ Dilatation and

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TABLE V. KERATITIS ROSACEA III
Group A=Specific Allergy Found

Treatment	Number	No Further Attacks in:		
		6 months	2 years	5 years
Desensitized by injection	42	36	34	34
Desensitized by mouth to food	8	4	4	4
Avoided allergens	28	25	20	18
	78	65 83%	58 71%	56 72%

TABLE VI. KERATITIS ROSACEA IV
Group B= Specific Allergy Not Found

DESENSITIZATION WITH HISTAMINE				
Total No.	No Further Attacks In:			5 years
	6 months	2 years	5 years	
22	15 70%	10 45%		9 41%

new formation of capillaries in upper third of the corium. Infiltration with small round cells and later with epitheloid cells and giant cells. This infiltration occasionally forms semi-translucent brown nodules of lupus vulgaris. Degeneration of elastic tissue in the papillary layer. Hypertrophy of the sebaceous glands. Later the nodules of infiltration break down into pus and many collections of polymorphs are then found in the corium in all stages of degeneration. Scarring follows the healing of these abscesses.]

In Group II one probably sees only scaly desquamation of the lids without permanent scarring; then in Group III there is engorgement of the vessels of both tarsal and bulbar conjunctiva accompanied by considerable irritation and some photophobia; the lacrimal flow is scanty and watery. If it becomes muco-purulent a secondary infection should be suspected, as the whiteropy discharge of hay-fever with its 70 per cent eosinophilia is not seen in uncomplicated rosacea. Occasionally grey nodules resembling those seen in phlyctenular-kerato-conjunctivitis appear on the bulbar conjunctiva. These nodules are surrounded by a typical network of varicosed vessels, and histologically are follicles of lymphocytes with epitheloid cells in the center. Similar nodules may sometimes be seen on the episclera.

The first sign that the cornea is involved (Group IV) is marginal vascular infiltration, which was described as a valuable diagnostic feature by Triehenstein.¹⁶ This infiltration is followed by development of subepithelial deposits and the assemblage of permanent scar tissue (Group V). For typical appearance of such lesions see Mr. Doggart's book, "Ocular Signs in Slit-lamp Microscopy" (London, 1949).

Numerous as the list of possible causes of keratitis rosacea may be, almost all authors agree that the condition is a "systemic rather than a

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local one." Digestive upsets, deficiency diseases and hormonal disorders all play a part, and must be treated appropriately, but even after all these have been corrected and the attack of the moment healed, there is still an underlying condition which predisposes to recurrence. As early as 1864 Arlt¹ recognized that ocular treatment was useless unless combined with treatment of the associated lesions of the face. A survey of investigation and treatment during the last ten years shows that allergy plays a fundamental part in the syndrome.

It cannot be emphasized too often or too strongly that every case of true rosacea is a potential candidate for the "blind" list. If possible before marginal vascular infiltration shows that the cornea is involved, a warning should be given.

From the preceding tables and the following case-sheets it becomes clear that if recurrences can be prevented, the vision will not deteriorate further; that is, *the condition will be arrested*. Case 2 is an example of those who, having had no treatment for the allergic condition, proceed to ultimate blindness; whereas in such cases as 3, 4 and 5, vision was arrested.

Case 2

<i>Lesion</i>	<i>Male, aged 45</i>	<i>Vision</i>
1930 lesions of face	R.E. 20/20	L.E. 20/20
1935 lesions of face + keratitis	20/30	20/60
1940 keratitis	20/120	20/200
1945 lesions of face + keratitis	20/120	nil
1949 lesions of face + keratitis	20/200	
No investigation or treatment in Allergy Department at any time.		

Case 3

<i>Lesion</i>	<i>Male, aged 52</i>	<i>Vision</i>
1932 lesions of face	R.E. 20/20	L.E. 20/20
1935 lesions of face + conjunctivitis	20/20	20/20
1939 lesions of face + conjunctivitis + corneal ulcer	20/30	20/20
1942 lesions of face + keratitis	20/60	20/60
1946 severe keratitis referred to Allergy Department**	20/200	20/120
1949 face and eyes quiet but cornea scarred	20/120	20/120

**Was desensitized in 1946 to feathers, cat-fur and house-dust.

DISCUSSION

Attention is drawn to the common denominator of all the cases reported above: underlying all of them, whether conjunctivitis, keratitis, iritis or glaucoma, is that elusive "allergic state," recently described by Williams¹⁰ as a "clinical phenomenon." Each physician's conception of this is perhaps as personal and varied as that of each individual patient.

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Case 4

<i>Lesion</i>	<i>Female, aged 64</i>	<i>Vision</i>	<i>L.E.</i>
1935 lesions of face	R.E. 20/20		20/20
1941 lesions of face + conjunctivitis	20/20		20/40
1946 lesions of face + conjunctivitis + keratitis	20/60		20/40
1947 lesions of face + keratitis	20/80		20/120
referred to Allergy Department**			
1950 face and eyes quiet but cornea scarred	20/80		20/80

**Desensitized by injection with allergens of orris root, feathers and house-dust in October, 1947.

Case 5

<i>Lesion</i>	<i>Female, aged 43</i>	<i>Vision</i>	<i>L.E.</i>
1930 lesions of face	R.E. 20/20		20/20
1933 lesions of face + conjunctivitis	20/20		20/20
1939 lesions of face + keratitis	20/30		20/60
1940 keratitis	20/60		20/120
referred to Allergy Department**			
1942 lesions of face + keratitis	20/30		20/120
1949 face and eyes quiet	20/30		20/120

**Complicated by myxedema. Has required thyroid therapy daily since 1939. Been desensitized with histamine three times in nine years.

Rosenow and Nickel¹³ published from the Mayo Clinic in 1932 some brilliant work on elective localization in determining the etiology of chronic iridocyclitis. They emphasized the development of hypersensitivity of the tissues due to remote foci of infection, e.g., of tonsils, teeth, prostate, or cervix. An important modern extension of this work comes from Stokes and Beerman¹⁵ of Philadelphia, and published this year in *Archives of Dermatology and Syphilology*. These authors write of a virus-pyogen sensitization sequence and make valuable suggestions for researches as soon as the appropriate viruses have been isolated, though they are fully aware of the importance of other elements of a complex background including other allergens, emotional stress, or exhaustion.

Whether we are faced with a typical phlyctenular conjunctivitis, a nodule of keratitis rosacea, or a reversible or indeed an irreversible dilatation of the vessels of the iris, one possibly common explanation exists, i.e., an allergic response to an *endogenous* toxin or allergen occurring typically in a patient with some metabolic instability. Perhaps it is not generally realized that *exogenous* dusts or pollens may be responsible for any or all of these manifestations, as often as bacterial proteins or food decomposition products.

From the work of Gutmann^{6,7} on conjunctivitis and spring catarrh (in which riboflavin appeared to enhance the action of adrenaline on small superficial vessels of the eye) and of Miles Atkinson⁹ on Ménierè's disease (in which he described two types of vertigo—rotational, helped by nicotinic acid, and positional, helped by riboflavine) it looks as if riboflavine is

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one of the substances capable of masking or neutralizing a metabolic weakness in epithelial cells favored by the strain of the allergic state (Pollak).¹²

Seventeen years ago A. L. Brown³ of Cincinnati, while working on considerations underlying experimental production of uveitis, suggested that the *recurrences* of iritis might represent "periods of hypersensitivity" and the *remissions* "periods of desensitization." The possibility of self-desensitization by human organisms might help to explain the periodicity of some allergic conditions, but until we have directed the full weight of our attention to understanding and possibly finding some way of compensating this allergic state of our patients, we are a very long way from being masters of our science.

ACKNOWLEDGMENT

I should like to record my appreciation of the generosity of the American College of Allergists in making possible my visit to the St. Louis conference; also to thank all those ophthalmologists who have allowed me to investigate and treat their patients. I am especially grateful to Mr. Humphrey Neame, Mr. Gayer Morgan, and Mr. Doggart, all of London, for permission to use drawings of their cases to demonstrate the appearance of typical allergic lesions of the cornea, and to Mr. Theodore Hamblin for his kind and courteous help throughout.

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24 Beaumont Street, Oxford, England

AEROSOLS III. AN INSPIRATION-TIME METER FOR QUANTITATIVE MEASUREMENT OF THE INHALATION PERIOD OF MISTS

H. A. ABRAMSON, M.D., F.A.C.A., H. H. GETTNER, M.A., and B. SKLAROFSKY, B.A.
New York, New York

IN a preceding communication¹ it has been shown with standard phenolsulfonphthalein aerosols that, using procedures of nebulization now in use, there are many variables involved in measuring the quantity of aerosol deposited in and absorbed from the lungs. It seemed desirable because of the extensive interest in therapeutic, toxic, and antigenic aerosols, to ascertain whether the reproducibility of the renal excretion of inhaled phenolsulfonphthalein mists was primarily dependent upon the time of and character of inspiration, other conditions being essentially constant. A stop watch was found to be unsuitable for measuring the exact time of inspiration. Some mechanical means of automatically recording the inspiration time was evidently required. An inspiration-time meter, for use with aerosols in general, is now described. Its application to the production of experimental asthma under more controlled conditions is demonstrated. With available data it will be shown, using comparatively simple equipment, (1) what the nature of the respiratory cycle during certain kinds of aerosol therapy is, and (2) how the time of inspiration of the aerosol administration can be more quantitatively measured. In this way, improvement in the technique of inhalation of aerosols is obtained by standardized and predictable procedures.

METHOD

In earlier unpublished experiments designed to follow the nature of the respiratory cycle during aerosol therapy, attempts were made to design equipment which would be activated directly by the patient's respiration, e.g., a thermocouple in the nebulizer-patient path. All of these attempts were unsatisfactory because of the difficulties of using the patient himself as the activating device. In the technique here described, the back pressure which is set up when the aerosol is generated by placing a finger over the cut-off valve (Figs. 1 and 2) is used to force a mercury column to establish a contact in the electric circuit maker, *A*. The circuit maker, *A*, establishes a current in the interval-timer, *B*, which flashes a light and acts as a supplementary timing device to the electric stop watch, *C*, equipped with an automatic brake. This stop watch can easily be read to a tenth of a second. The total period of inspiration as well as each individual inspira-

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From the First Medical Service and Laboratories of the Mount Sinai Hospital, New York, N. Y.

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tion is readily read on the dial of the stop watch and recorded. The stop watch is connected to a special outlet in the interval-timer, *B*. In addition to the stop watch there is also an electric counter, *D*, which simultaneously records the number of inspirations. This equipment is designed for re-

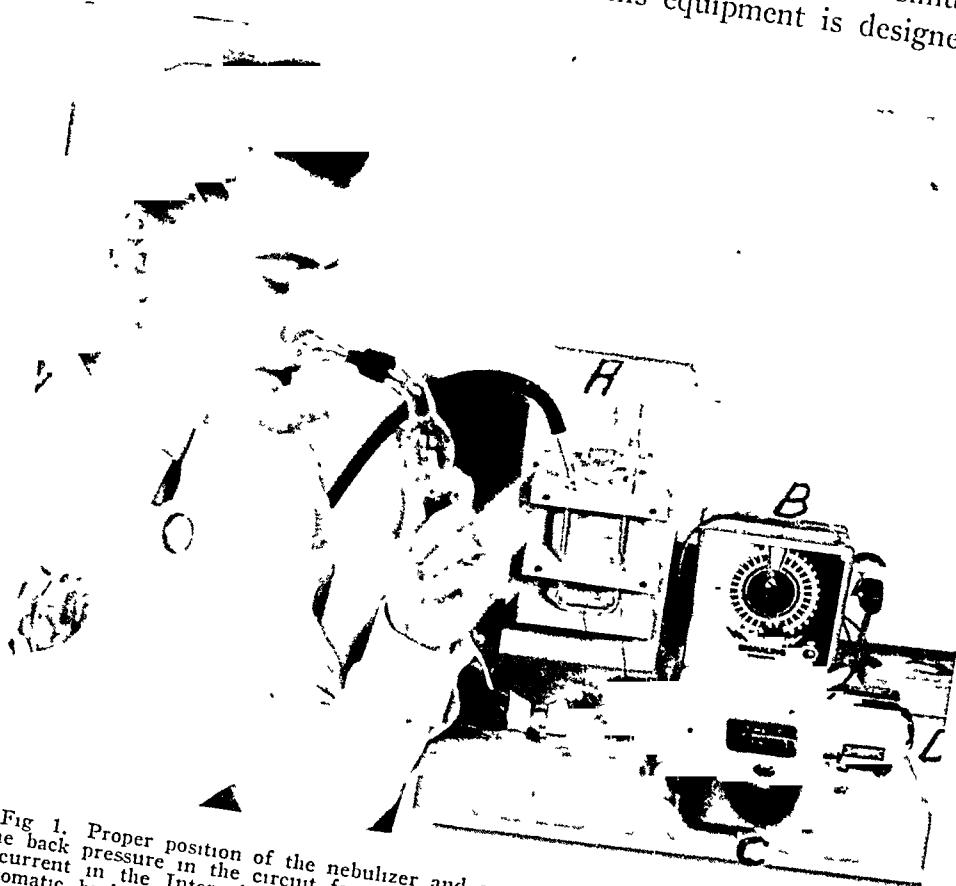


Fig. 1. Proper position of the nebulizer and components of the Inspiration-Time Meter. The back pressure in the circuit forces a mercury column in the U-tube, *A*, to establish a current in the Interval Timer, *B*. The electric stop watch, *C*, is equipped with an automatic brake. A counter, *D*, gives the number of inspirations. This arrangement is convenient for research purposes. For routine therapy neither the Interval Timer, *B*, nor the counter, *D*, is required. The circuit maker, *A*, may be attached directly to the electric stop watch, *C*.

search purposes; for therapeutic purposes, neither the interval-timer, *B*, nor the electric counter, *D*, is required. All that are necessary for routine therapy are the circuit-maker and the stop watch *C*. For example, in quantitative therapeutic procedures, the nurse may merely be told to administer for 50 seconds a solution of glycerite of epinephrine 1:100, or 500 seconds of penicillin aerosol at a given volume-velocity of oxygen. In this way the actual time which the patient inspires the material may be simply recorded. The total time of experiment is measured by a manually controlled stop watch.

It is evident that the inspiration-time meter, as illustrated in Figures 1 and 2, can also be used (1) to control the amount of aerosol administered in producing experimental asthma with histamine, acetylcholine compounds and allergens like ragweed solutions, and (2) with the therapeutic agent to estimate the quantity of inspired aerosol administered to control the

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asthma. By using an inspiration-time meter of this type, many of the contradictory statements found in the current aerosol literature, based upon experiments consisting of a small number of squeezes of a nebulizer bulb to deliver the agent studied, may be clarified.

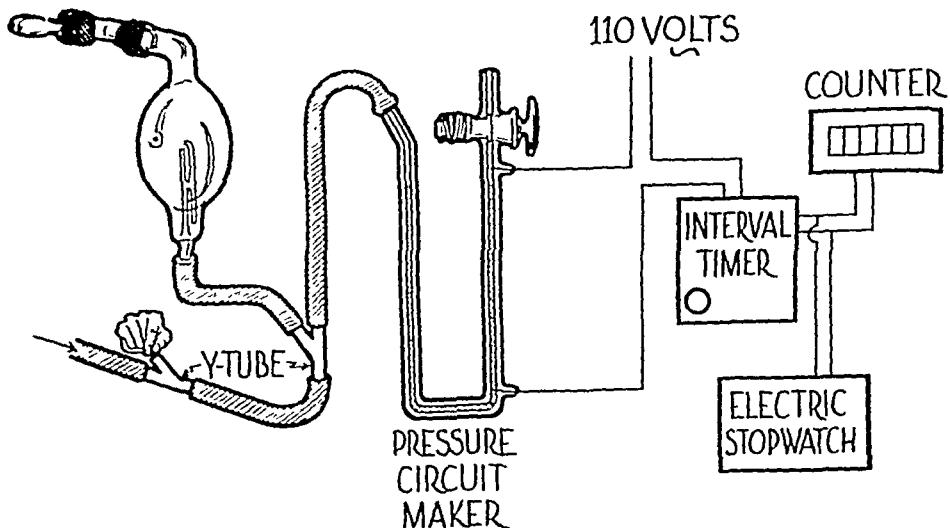


Fig. 2. This diagrammatically illustrates the Inspiration-Time Meter shown in Figure 1. As the finger occludes the Y tube, gas is forced through the atomizing unit in the nebulizer. This establishes a back pressure which forcibly thrusts the mercury column upward against the pressure stop cock. This establishes the electric circuit, thus simultaneously activating the Interval-Timer (30 minutes total time), the electric stop watch and the counter.

TABLE I

All experiments in this group were performed on a male subject, B. S. Vital capacity 4.8 liters. Weight 187 pounds; height 5 feet 11 inches. Inspiration time was measured with the Inspiration-Time Meter. Phenolsulfonphthalein solution contained 68 mg. per c.c. Sufficient solution (1 to 5 c.c.) was initially placed in the nebulizer dependent on the inspiration time of experiment. Volume velocities of oxygen are flowmeter readings (uncorrected) at the tank between 8 and 9 liters per minute.

1 Expt. No.	2 Date	3 Total Time Sec.	4 Inspiration Time Sec.	5 Average Inspiration Time Sec.	6 Number Inspirations	7 Dye Excreted in 2 hrs. mg.	8 Ratio: Insp. Time Total Time
IT-1	4/19	300	183	5.9	31	0.88	0.61
IT-2	4/20	600	348	4.8	73	3.55	0.58
IT-5	4/27	300	205	7.1	29	1.70	0.68
IT-6	4/28	600	363	5.3	68	3.50	0.60
IT-7	4/29	900	553	5.2	106	7.0	0.61
IT-10	5/25	490	300	7.6	39	2.66	0.61
IT-12	5/30	840	500	6.1	82	10.20	0.59
IT-17	6/17	160	100	7.1	14	0.60	0.62

EXPERIMENTAL

Using the inspiration-time meter, experiments on the urinary excretion of 5 per cent phenolsulfonphthalein solution inhaled as an aerosol was studied on B.S. from 100 seconds to 553 seconds. The data of these experiments are given in Table I. The average inspiration time is prolonged so that the ratio of the inspiration time to the total time is close to 0.6 or more. The dye excreted in two hours varied from 0.6 mg to 10.2 mg.

Since the method has an inherent error of 0.2 to 0.4 mg due to the pigments in the urine, the lower values are only approximate. To establish relationship between inspiration time and dye excreted in two hours, the data obtained on this one subject, B. S., from Table I, are plotted in Figure 3, up

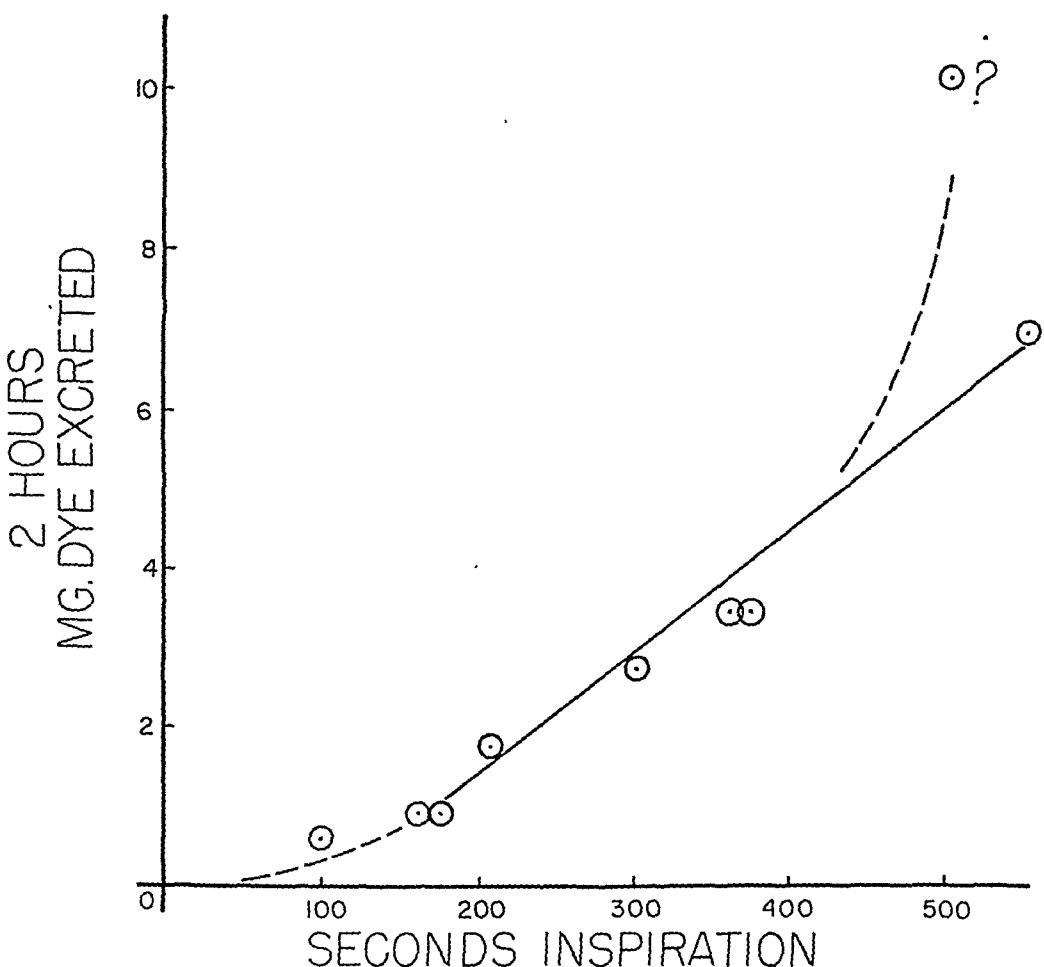


Fig. 3. The data obtained on one subject, B. S., from Table I are plotted in this figure, up to 553 seconds of inspiration time. Seven random experiments fall on a straight line. If the linear relationship extrapolated to zero dye excretion, there would be a threshold of excretion at 120 seconds. However, this is not true because at 100 seconds an appreciable amount of dye appears in the urine. The excretion of the dye, therefore, rises fairly slowly with inspiration time up to about 170 seconds, a linear relationship then appearing for the next 300 seconds. The point off the curve with the question mark at about 500 seconds cannot be explained at present.

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A typical experiment performed on B. S. with the dye is illustrated in Table II. The general outline of Table II may be used to plan experiments

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TABLE II. TYPICAL INSPIRATION-TIME METER EXPERIMENT ON LUNG CLEARANCE

A. SUBJECT: B. S.

Expt. No. IT-15, 6/10, started at 10:30 A.M.

A DeVilbiss No. 40 nebulizer was used with nasal tips and L-tube with the vent closed. The initial volume of phenolsulfonphthalein was 3 c.c., each c.c. containing 47.0 mg. (total dye—141 mg.). A volume velocity of 8 liters per minute was used.

A benzedrine inhaler was used to shrink the nasal mucosa. The bladder was emptied followed by drinking 500 c.c. water.

B. INSPIRATION CHARACTERISTICS

Total number of inspirations.....	69
Average inspiration.....	7.2 seconds
Total inspiration time.....	500 "
Total experiment time.....	780 "

Inspiration Time

$$\text{Ratio: } \frac{\text{IT}}{\text{TT}} = 0.62$$

Total Time

C. DELIVERY

Nebulizer residue.....	55 mg.
Deposit in L-tube.....	11 mg.
Deposit in nasal tips.....	11.4 mg.
Total residue.....	77.4 mg.
Delivered to subject:	63.6 mg.

D. EXCRETION OF DYE IN THE URINE

Specimen	Time	Vol. of Urine	Mg. Dyes
1st	½ hour	25 c.c.	0.97
2nd	1 hour	30 c.c.	2.40
3rd	2 hours	45 c.c.	2.48
4th	3 hours	50 c.c.	1.52
5th	4 hours	80 c.c.	0.93
6th	5 hours	60 c.c.	0.27
 Total dye excreted:			8.57

E. INDIVIDUAL INSPIRATIONS

Column 1 is the inspiration number. Column 2 is the reading on the stop watch. Column 3 gives the duration of inspiration in seconds.

1.	2.	3.	1.	2.	3.	1.	2.	3.
1.	12.1	12.1	24.	178.5	8.7	47.	362.8	7.0
2.	23.1	11.1	25.	189.1	10.6	48.	370.6	7.8
3.	31.3	8.2	26.	197.8	8.7	49.	378.9	8.3
4.	38.4	7.1	27.	204.8	7.0	50.	385.3	6.4
5.	45.3	6.9	28.	212.2	7.4	51.	393.0	7.7
6.	54.1	8.8	29.	220.0	7.8	52.	399.5	6.5
7.	61.2	7.1	30.	228.0	8.0	53.	404.7	5.2
8.	65.7	4.5	31.	236.7	8.7	54.	410.5	5.8
9.	73.1	7.4	32.	245.9	9.2	55.	416.0	5.5
10.	81.1	8.0	33.	253.1	7.2	56.	421.8	5.8
11.	87.8	6.7	34.	261.5	8.4	57.	427.0	5.2
12.	93.7	5.9	35.	268.8	7.3	58.	433.0	6.0
13.	99.8	6.1	36.	276.5	7.7	59.	437.2	4.2
14.	106.5	6.7	37.	284.3	7.8	60.	443.6	6.4
15.	113.4	6.9	38.	291.9	7.6	61.	448.0	4.6
16.	119.9	6.5	39.	301.2	9.3	62.	453.2	5.2
17.	126.7	6.8	40.	309.1	7.9	63.	459.3	6.1
18.	134.0	7.3	41.	317.6	8.5	64.	467.4	8.1
19.	141.3	7.3	42.	325.6	8.0	65.	474.5	7.1
20.	148.3	7.0	43.	333.4	7.8	66.	482.1	7.6
21.	156.1	7.8	44.	341.1	7.7	67.	488.9	6.8
22.	163.0	6.9	45.	348.3	7.2	68.	495.4	6.5
23.	169.8	6.8	46.	355.8	7.5	69.	500.2	4.8

on the delivery of aerosols and need not be restricted to dyes. A similar form can be used with histamine, mecholyl, allergens, or penicillin aerosols as well as sympathomimetic amines. Note in Table II the following points: the volume of 8 liters of oxygen per minute (Section A) is uncorrected and might be slightly higher (about 10 per cent). In comparing therapeutic aerosols similar to sympathomimetic amines, this value should be more

precisely obtained.' The total number of inspirations in the experiment in Table II was sixty-nine (Section B) with the average inspiration time, 7.2 seconds. It is of interest that, in general, the total inspiration time (Table I) shows that with this technic the ratio of inspiration time to total

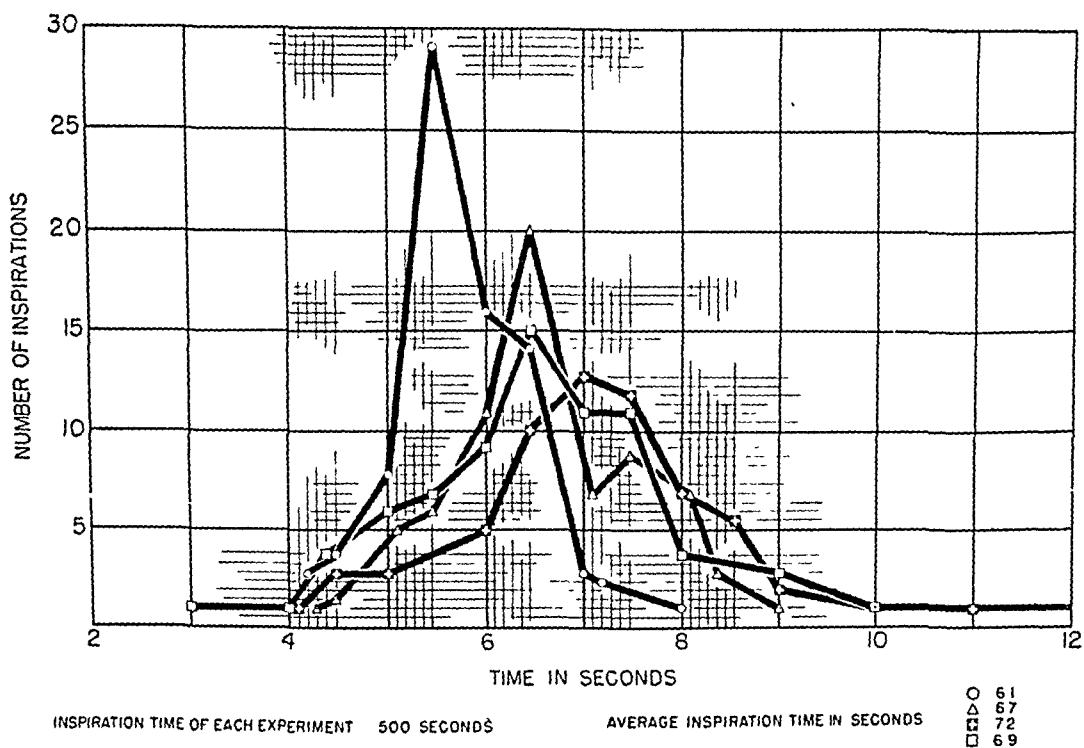


Fig. 4. Population distribution curves of the inspiration times on one subject, B. S.

time is prolonged, thus automatically increasing the probability of deposition in the lungs. Forty-five per cent of the dye originally contained in the nebulizer (Section C) was delivered to the subject. Some of the dye, as mentioned hitherto, is deposited in the nose. Nevertheless, at least 8.57 mg of the dye were excreted in the urine in five hours. This amounts to 13 per cent of that delivered to the subject. In other experiments this value has been higher. Since a certain amount of the dye is lost following intravenous administration (approximately 30 per cent), and since the inhalation of aerosols is somewhat similar to intravenous administration of the dye, we may conclude from this experiment that at least 15 per cent of the dye delivered to the subject passed through the lungs. This value, although low, is definite and shows that antibiotics and other drugs used in aerosol therapy may be subjected to precise independent study by this technic. Section E, Table II, lists in detail the number of inspirations, the reading, and the duration of single inspirations. In general, this experiment is typical of the variations found on inspiration.

Distribution of Inspirations on Subject B. S.—Section E in Table II illustrates how the time of individual inspirations can be accurately recorded during the inspiration of aerosols. Four experiments on B. S.

with a total inspiration time of 500 seconds were studied in this way. The inspirations were then grouped according to inspiration times given in Figure 4 and plotted against the number of inspirations to obtain the distribution curves of the inspiration times of B. S. The inspiration times of this subject vary from about six to seven seconds, as illustrated in the Figure, and give somewhat skewed distribution curves, the significance of which on this subject is unknown. Shorter average inspiration times were observed, e.g., as low as two seconds in anxiety states. The distribution curves, therefore, as shown in Figure 4, may also be connected with the mental state of the patient as well as with the physiological character of the respiration and the mechanical characteristics of the inspiration-time meter. Distribution curves of this type for physiological or psychodynamic studies can readily be obtained by having the patient breathe oxygen alone or physiological saline through the nebulizer. The device, therefore, is another way of studying the breathing pattern of the individual under conditions simulating aerosol therapy by the nasal route.

EXPERIMENTAL HISTAMINE ASTHMA

Data in the literature purporting to describe the comparative effects of therapeutic aerosols in a quantitatively evaluated fashion may often be erroneous. When three or four inhalations are given with the nebulizer and an aerosol is produced in the usual qualitative way for the patient to inhale, obviously only rough approximations can be given. Thus, in a recent paper which evaluates isopropyl epinephrine in comparison with other sympathomimetic amines, no quantitative data on inspiration is given and conclusions are open to serious question. The inspiration-time meter is designed to overcome errors of this type because it employs an essentially closed system. In any particular patient, the error will be fairly constant and dependent essentially on that produced by the loss due to deposition in the nose and oropharynx, provided the experimenter keeps other factors in mind. These factors are: (1) the particle size distribution, (2) the average inspiration time, and (3) the volume velocity with which a known quantity of the aerosol is administered and controlled. These factors can be reproduced fairly well in the same patient.

The following experiments with histamine aerosols are presented to illustrate the type of experiment which is possible with the inspiration-time meter.

Histamine diphosphate was dissolved in water containing 10 per cent of glycerine to bring it to the desired concentration. The glycerine was added to insure that the particle size distribution would remain fairly constant. As pointed out previously, 30 per cent glycerine was optimal, but it was decided that 10 per cent would suffice for the present experiments. In using a DeVilbiss No. 40 nebulizer and nasal tips with the L-tube (with vent open), a volume velocity of 7 to 9 liters per minute of oxygen was employed. In this early series the vent was kept open to facilitate the pa-

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In all the experiments, the DeVilbiss No. 40 nebulizer was used with nasal tips and L-tube. The total inspiration time was the initial volume. The vent was open and the volume velocity was 200 seconds unless otherwise noted. 7½ and 8½ Experiments were done during the winter.

TABLE III. HISTAMINE AEROSOL

Patient	2.	3.	10% Glycerine Solution	Average Vital Capacity in Cubic Centimeters (Three readings each)				5. Av. time of each inspiration in seconds	6. Number of inspirations	7. Total time of expt. in seconds	8. Symptoms
				Before Aerosol	After 50 sec.*	After 100 sec.*	After 150 sec.*				
M.M.(1)	Ragweed Hay fever	1:5,000 Histamine	3700	3650	3700	3700	3700	200 sec.*	6	—	None
			3480	3410	3650	3650	3260				
D.F.(1)	Asthma Allergy; Ragweed, etc.	1:5,000 Histamine	3100	1900	After 32 seconds chest as in beginning of asthmatic attack. 0.2 c.c. epinephrine given. Vital capacity 10 min. later—3150**	3580	8	1.3	25	—	None
			2460	2630							
F.R.(1)	Asthma when excited Dust-sensitive	1:5,000 Histamine	2570	2500	2480	2450	2580	2.5	80	337	None
			2350	2850	2800	2750	2800				
H.K.(1)	Bronchial asthma Cor pulmonale	1:5,000 Histamine	2350	2700	2650	2600	2700	3.5	57	374	Running nose no tightness in chest Sneezing, Running nose
			710	After 16 sec. capacity—513 c.c.* Relieved with 0.2 c.c. epinephrine.	Vital capacity 16 sec. tightness in chest. Relieved with 0.2 c.c. epinephrine.	4	4				

* Inspiration time in seconds.

tients' breathing. In subsequent experiments the vent was closed. The vital capacity was taken in triplicate with a Buhl spirometer before the experiment and then in triplicate at 50-second intervals. Asthmatic patients who responded, however, usually were unable to take the 200 seconds of inspiration time. If asthma or tightness in the chest occurred, the experiment was stopped, the vital capacity was taken and 0.2 c.c. of 1:1000 epinephrine solution by hypodermic injection was administered. If there were no untoward reactions to 1:5000 histamine, the patient was given 1:500 at a subsequent visit and not immediately following.

To illustrate the use of the inspiration-time meter in producing asthma with histamine aerosol, the type of data which may be obtained are given in Table III. Thus Patient M. M., who is a typical ragweed hay fever patient, was able to take during the winter, when these experiments were done, both 1:5000 and 1:500 histamine aerosols on repeated occasions for 200 seconds of inspiration time with no change in vital capacity. In addition, except for a stuffy nose there were no other symptoms. On Patient M. M. the average time of each inspiration varied between 6 and 8 seconds. Patient D. F., on the other hand, who had clinical asthma as well as sensitivity to ragweed, responded to 1:5000 histamine after 32 seconds with heaviness in the chest and a reduction in vital capacity from 3100 c.c. to 1900 c.c. Ten minutes after 0.2 c.c. of epinephrine was given, the vital capacity was restored to 3150 c.c. It is of interest that this patient must have retained comparatively much less histamine than Patient M. M., because the average inspiration time was only about 2 seconds. With so short an inspiration time (32 seconds) and with a volume velocity of about 8 liters per minute in the closed system which was employed, the patient can inspire only about 150 c.c. per second. This patient, therefore, on each inspiration inspires only 200 c.c. of a gas-oxygen-aerosol mixture under our conditions. Only a fraction of this volume reaches the recesses of the lungs. It should be noted that when physiological saline was used, the change produced by 1:5000 histamine is no longer observed, the average inspiration time increasing to 2.5 seconds with the inverse ratio of inspiration to expiration still prolonged. A rather interesting example is F. R., who has severe asthma especially under emotional stress. In this patient, although there were some nasal symptoms caused by the histamine, the 1:500 histamine on two occasions produced no decrease in vital capacity. The ratio of inspiration time to expiration time was, as found with our technic, higher than 0.5. This is evident from inspection of columns 4, 5, 6, and 7, with the ratios of 200 to 374, 302, and 281 seconds, respectively. Patient H. K. responded immediately to 1:5000 histamine. This patient with bronchial asthma and cor pulmonale was anoxic to begin with. Her vital capacity was 710 c.c. and dropped to 513 c.c. after 16 seconds of 1:5000 histamine. However, the patient recovered immediately following a small dose of epinephrine. Administration of epinephrine aerosol in this patient did not increase the vital capacity above 1000 c.c. The patient subsequently

made a fair recovery in an oxygen tent, the vital capacity still remaining below 1000 c.c.

In certain patients, similar to patients D. F. in Table III, there is a marked change in vital capacity with few if any sibilant or sonorous râles appearing in the chest. In other words, histamine asthma is produced in all likelihood by spasm of the bronchial tubes having fairly large diameters. Histamine asthma of this type is similar to the preasthmatic sensation of constriction and heaviness in the chest so often complained of before the wheezing respiratory sounds are audible.

DISCUSSION

The method herein described has several defects which have already been noted. These are losses due to dispersion in the nasal passages, swallowing, and exhalation of particles. On the other hand, the advantages offered by the present technic are made clear by a closer scrutiny of the data in Table III. The subject breathed in 8 liters of oxygen per minute for an inspiration time of 8.33 minutes. We know, therefore, that the subject breathed 66.6 liters of oxygen and, therefore, of aerosol, during this time. Since the average inspiration was 7.2 seconds, and since the subject breathed 136 c.c. of oxygen per second, each inspiration amounted to approximately 980 c.c. of the aerosol. In terms of delivery to the subject it is likely that at least 9 mg. of PSP were deposited in the lungs during sixty-nine inspirations, or about 0.13 mg of dye was available for passage through the lung barrier per average inspiration. It seems likely that the method, therefore, provides a controllable technic of studying lung clearance by means of determinations of the dye or of para-aminohippuric acid in the urine. It is believed that through study of the curve of urine values against delivery values, more precise data on the nature of the lung barrier and the effects of drugs on this barrier during aerosol therapy may be achieved. Blood values if obtainable would be preferable.

The variability in the response of asthmatic patients (to be described in a future communication) to histamine aerosol under those controlled conditions has led to the assumption that within the dose range established only certain asthmatics will respond to histamine with a diminution in vital capacity. Preliminary data indicate that asthma is more readily produced in individuals whose asthma is more closely connected with immunologic than with psychologic factors. Where emotional upsets produce asthma, as evidenced in our series thus far, histamine aerosol does not as readily produce a change in vital capacity. Although our data are insufficient, they, nevertheless, suggest that an unbalanced or sensitized bronchial tube is more sensitive to histamine and other spasm-producing substances and that this sensitivity is not as dependent upon the emotional pattern of the patient as upon the immunologic state of the tissues involved.

INSPIRATION-TIME METER—ABRAMSON ET AL

SUMMARY

1. A technique for measurement of the time taken for inspiring aerosols is described. The device consists essentially of an electric circuit-maker which is activated by the back pressure that is set up when the aerosol is inspired.

2. By this method (a) the total number of inspirations, (b) the average inspiration time, the total inspiration time, (c) the population distribution of inspirations, and (d) the ratio of the inspiration time to total time of respiration, are obtained.

3. A typical experiment on lung clearance of phenolsulfonphthalein aerosol as a function of inspiration time is given. It is shown that within the limits of experimental error, there may be a linear relationship between the weight of dye excreted in two hours and the inspiration time between 200 and 400 seconds. By this technique it is demonstrated that under certain conditions approximately 15 to 20 per cent of dye clears the lung barriers and is excreted in the urine.

4. Experiments on the production of histamine asthma with this technique provide a reproducible procedure for the induction of experimental asthma under semi-quantitative conditions and its control by therapeutic agents.

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133 East 58th Street

CLINICAL EXPERIENCE WITH CHLOR-TRIMETON IN HAY FEVER AND OTHER ALLERGIES

G. EVERETT GAILLARD, M.D., F.A.C.A.
White Plains, New York

THE high therapeutic index and low toxicity reported for the anti-histamine, Chlor-Trimeton maleate,² brand of chlorprophenpyridamine maleate, prompted this investigation to determine its effectiveness in a variety of allergic disorders. Chemically the compound is 1-(*p*-chlorophenyl)-1-(2-pyridyl)-2-N, N-dimethylpropylamine maleate. It is the maleic acid salt of a new compound derived by halogenating the antihistaminic substance, Trimeton, brand of prophenpyridamine.

The clinical reports on Chlor-Trimeton maleate to date have shown it to possess high therapeutic efficacy and have confirmed its low toxicity in man.^{1,3}

CLINICAL MATERIAL

In the present series Chlor-Trimeton maleate* was administered to 332 office patients. The patients sensitive to inhalant allergens were receiving standard hyposensitizing injections. The conditions from which they suffered were as follows: hay fever; hay fever accompanied by asthma; pollen, mixed and infective asthma; vasomotor rhinitis of allergic, infective, and of unknown origin; urticaria; and several miscellaneous affections potentially of allergic origin. All of the cases were seen in private practice, and the results were tabulated on several successive visits. Since many of the patients had more than one symptom picture, the tabulated results were observed in over 550 symptoms or syndromes.

DOSAGE

The dosage of Chlor-Trimeton maleate required to alleviate allergic symptoms appeared to be 2 to 4 mg. orally given from two to four times daily, with the usual dosage being between 6 and 20 mg. daily. In a variety of allergic disorders, Allison and Robinson¹ obtained satisfactory relief in twenty-six of thirty-six patients (72.2 per cent) with doses of Chlor-Trimeton maleate in this range three times a day. Vickers and Barrett³ found the optimal dosage in seasonal hay fever to be 6 to 16 mg. per day in divided doses. In an attempt to determine the optimal dosage, 1, 2, 4, and 8 mg. three times daily were administered to eight, 157, 158, and nine patients, respectively.

TABULATION OF RESULTS

Table I records the results with these dosages in the various conditions. Strangely, there was no response in the nine patients in which doses of 8

*Chlor-Trimeton maleate was supplied by Schering Corporation, Bloomfield, New Jersey. Presented at the Sixth Annual Meeting of The American College of Allergists, January 15-18, 1950, St. Louis, Missouri.

CHLOR-TRIMETON IN HAY FEVER—GAILLARD

TABLE I. CLINICAL RESULTS WITH CHLOR-TRIMETON MALEATE
IN ALLERGIC DISORDERS

Type of Allergy	No. of Cases	CLINICAL RESULT: NUMBER OF CASES											
		1 mg.			2 mg. q.i.d.			4 mg. t. or q.i.d.			8 mg. t. or q.i.d.		
		Good	Fair	Poor	Good	Fair	Poor	Good	Fair	Poor	Good	Fair	Poor
Hay fever, total	247	2	5	3	47	54	21	27	62	26			3
Hay fever with asthma	85	1	3		9	23	6	3	27	12			1

RESULTS—DOSAGE 2 TO 4 mg. q.i.d.

	No. of Cases	Good	Fair	Poor	
Pollen asthma	29	10	12	7	
Mixed (allergic and infective) asthma	66	2	52	12	
Infective (intrinsic) asthma	46	0	9	37	
Vasomotor rhinitis—allergic, infective, and unknown etiology	30	4	17	9	Good: 75-100% relief of symptoms
Angio-edema and urticaria	10	1	6	3	Fair: 50- 75% relief of symptoms
Eczema and dermatitis	16	0	1	15	Poor: 0- 50% relief of symptoms
Vertigo due to pollen	1	1	0	0	
Migraine	4	0	1	3	

TABLE II. ONSET AND DURATION OF THE EFFECT
OF CHLOR-TRIMETON MALEATE

ONSET												
Time in Minutes												
Dosage	No. of Patients Reporting	15		15-30		30-60		No.	%	No.	%	
		No.	%	No.	%	No.	%					
2 mg. 4 mg.	59 73	23 33	39.0 45.2	26 25	44.0 34.2	10 15	17.0 20.6					

DURATION													
Time in Hours													
Dosage	No. of Patients Reporting	2-4		4-8		8-12		12-24		Over 24		No.	%
		No.	%	No.	%	No.	%	No.	%	No.	%		
2 mg. 4 mg.	108 92	15 17	13.9 18.5	47 34	45.3 37.0	24 27	22.2 29.4	21 13	19.4 14.1	1 1	Less than one 1.0		

mg. three times daily were tried. When symptoms disappeared completely following administration of Chlor-Trimeton maleate, that is with 75 to 100 per cent relief, the result was called good. When relief of symptoms was partial, from 50 to 75 per cent, it was recorded fair. Poor results were those in which less than 50 per cent relief or none was obtained.

ONSET AND DURATION

Fifty-nine of the 157 persons receiving 2 mg. of Chlor-Trimeton maleate per dose were able to determine the time of onset of the effect of the medication. Twenty-three (39 per cent) became aware of it within fifteen minutes, twenty-six (44 per cent) within fifteen to thirty minutes. Among those receiving 4 mg. per dose, a slightly higher percentage noticed the

CHLOR-TRIMETON IN HAY FEVER—GAILLARD

TABLE III. COMPARISON OF RESULTS WITH DOSAGES
OF 2 AND 4 MG. OF CHLOR-TRIMETON MALEATE

Type of Allergy	2 mg. t.i.d.				4 mg. t.i.d.						
	Total No. Cases	Improved		Not Improved		Total No. Cases	Improved		Not Improved		
		No.	%	No.	%		No.	%	No.	%	
Hay fever, total	122	101	82.8	21	17.2	115	89	77.4	26	22.6	
2-4 mg. t.i.d.											
Type of Allergy	Total No. Cases	Improved		Not Improved		Total No. Cases	Improved		Not Improved		
		No.	%	No.	%		No.	%	No.	%	
Pollen asthma	29	22	76	7	24						
Mixed (allergic and infective) asthma	66	54	81	12	18					Improved: 50-100% relief of symptoms	
Infective (intrinsic) asthma	46	9	20	37	80					Not Improved: 0-50% relief of symptoms	
Vasomotor rhinitis	30	21	70	9	30						
Urticaria	10	7	70	3	30						
All others	21	3	15	18	85						

effect within fifteen minutes. It appeared in approximately 80 per cent within thirty minutes. The effect was apparent in all patients reporting in both groups within an hour, as shown in Table II.

One hundred and eight persons receiving the 2 mg. dosage and ninety-two of those receiving 4 mg. reported the duration of the effect of Chlor-Trimeton maleate. There was no significant difference in the two groups, the effect with the 2 mg. dosage lasting as long as that with twice the amount.

The 247 patients with seasonal hay fever comprised the largest group treated. Among the 122 of them who received Chlor-Trimeton maleate in 2 mg. doses, 101 (83 per cent) showed improvement consisting of 50 to 100 per cent relief of the mucous membrane inflammation and nasal discharge characteristic of hay fever. Only twenty-one (17 per cent) showed no improvement. These percentages are slightly better than those obtained when 4 mg. were given to 115 patients in the hay fever group. Table III presents this comparison. Two hay fever patients received one mg. three times a day. One responded to this minute dose with complete relief of symptoms, the other with partial relief. In the former the antihistamine effect lasted for six to twelve hours. In the latter, appearance of the effect was delayed but it lasted for four to six hours.

As may have been expected, the asthmatics of the infective or intrinsic etiology were helped little or not at all by the drug. Among these nine (20 per cent) reported some degree of relief, while thirty-seven (80 per cent) reported little or no help. On the other hand, those asthmatics in whom extrinsic factors were wholly or partly responsible for their symptoms were benefited by the drug. Where the extrinsic factors were, as far as could be determined, the sole contributing cause, as in the pollen asthmatics, 35 per cent had good results, 41 per cent fair results and 24 per cent poor results from the use of Chlor-Trimeton maleate. Where the extrinsic etiological factors were accompanied by infection, the good results were only 3 per

CHLOR-TRIMETON IN HAY FEVER—GAILLARD

TABLE IV. SIDE REACTIONS

	1 mg.		2 mg.		4 mg.		Total	
	Mild	Severe	Mild	Severe	Mild	Severe	Mild	Severe
Drowsiness	1		15	1	9	2	25	3
Vertigo			1		1		2	
Headache					1	1	1	1
Gastrointestinal upset					2		2	
Grogginess			1					1
Lightheadedness			1					1
Difficulty in focusing			1					1
Diarrhea			1					1
Listlessness			1					1
Shakiness			1					1
Nervousness			1					1
Disturbing dreams			1					1
Dry throat, cough					1			1
Aggravation of chief complaint		1*			1**		2	

*Eczema.

**Hay fever with eczema.

cent, while the fair results were 78 per cent and the poor results only 18 per cent.

Considering all the cases of hay fever together, 101 (82.8 per cent) of the 122 receiving the 2 mg. dosage improved, as shown in Table III. Satisfactory improvement also was obtained with 4 mg. of Chlor-Trimeton maleate in eighty-nine (77.4 per cent) of the 115 receiving this dosage. It would appear, therefore, that the compound represents a highly effective agent for control of the symptoms of this allergic manifestation, and that a dose no larger than 4 mg. suffices to produce the effect.

Table III also shows the effectiveness of Chlor-Trimeton maleate in vasomotor rhinitis. The small number of patients warrants no conclusions, but improvement in twenty-one of thirty seems to indicate that it is effective. Concomitant rash and cough in two patients were not improved.

Too few persons with urticaria, eczema, dermatitis, or migraine presented themselves for an accurate evaluation of the worth of Chlor-Trimeton maleate in these disorders. Four mg. brought partial relief of itching and partial disappearance of the eruption in seven persons with urticaria. Fifteen with eczema or dermatitis and three with migraine showed little or no improvement.

SIDE REACTIONS

Thirty-six mild reactions occurred in the series, an incidence of 10.8 per cent. The most frequent reaction was slight drowsiness which followed the administration of 2 mg. in fifteen persons, and the administration of 4 mg. in nine. One in the 2 mg. group also experienced vertigo, and this reaction occurred once with the larger dose. Two persons receiving 4 mg. had a gastrointestinal upset. Other mild reactions occurred one time each.

Of the four persons treated who had more intense reactions to the drug, headache forced one to discontinue its use. The other three were very

(Continued on Page 327)

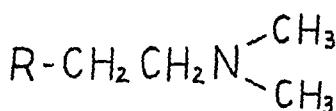
THE ANTIHISTAMINIC DRUGS

Their Relationship as Shown by the Structural Formulas

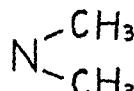
L. E. SEYLER, M.D., F.A.C.A.
Dayton, Ohio

IN THE PAST three years an even dozen antihistaminic drugs have been placed on the market for the control of allergic symptoms. The purpose of this paper is to emphasize their relationship as shown by their structural formulas.

The structural formula common to almost all of them could be represented as follows:



Here R is any large slightly basic radical representing 75 per cent of the molecular weight of the compound. The



does the blocking of the histamine from the receptor positions in the tissue cells. Hence this dimethyl amino group gives the maximum antihistaminic activity attained by the compounds so far discovered. Efforts to improve the action of the compounds by changing the side chains of the carbon atoms of the ethylene groups have not been practical. Therefore this part of the formula has remained the same in eleven of the antihistaminic compounds.

The first differentiation that has been made is in the first atom attached to the ethylene radical, as shown by these examples:

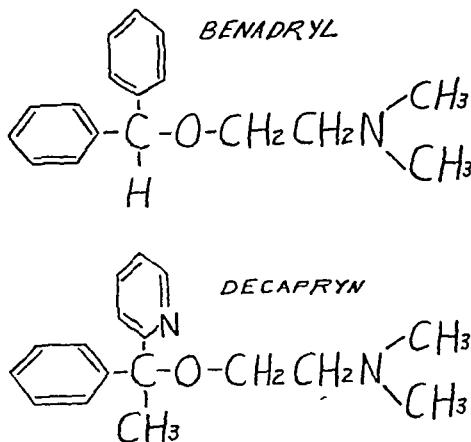
	DROWSINESS	ACTIVITY	TOXICITY
$R-\text{O}-\text{CH}_2\text{CH}_2\text{N} \begin{matrix} \diagup \text{CH}_3 \\ \diagdown \text{CH}_3 \end{matrix}$	1	1	2
$R-\text{N}-\text{CH}_2\text{CH}_2\text{N} \begin{matrix} \diagup \text{CH}_3 \\ \diagdown \text{CH}_3 \end{matrix}$	2	2	1
$R-\text{CH}_2-\text{CH}_2\text{CH}_2\text{N} \begin{matrix} \diagup \text{CH}_3 \\ \diagdown \text{CH}_3 \end{matrix}$	3	3	3

Presented at the Fifth Annual Meeting of The American College of Allergists, April 14-17, 1949,
Chicago, Illinois.

THE ANTIHISTAMINIC DRUGS—SEYLER

Here we see that comparing the three types of compounds the attachment of an atom of oxygen causes the greatest toxicity and drowsiness and is second best in antihistaminic activity in animal experiments. The attachment of an atom of nitrogen results in the best antihistaminic activity and causes less toxicity and drowsiness. The attachment of a methyl radical gives the third best antihistaminic activity and causes the least toxicity and drowsiness.

The two commercial compounds having the oxygen atom attached to the dimethyl amino ethylene are Benadryl (dimethyl amino ethyl benzohydryl ether) and Decapryl (dimethyl amino ethoxy methyl benzyl pyridine). Hydrillin is a Benadryl base combined with aminophylline.



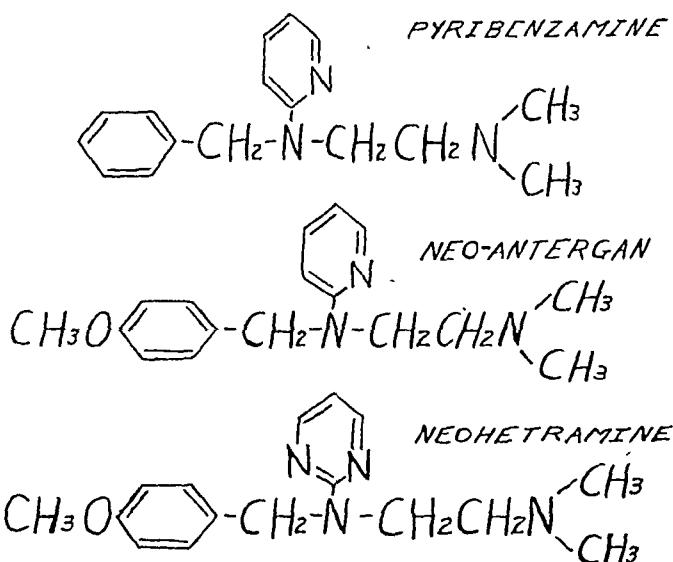
By animal experiment these two compounds, as would be expected by the slight difference in their structural formulas, are very similar in activity, but Decapryl is also more toxic on animals though it causes less sedation. Clinically the Decapryl seems to be effective in smaller doses, and therefore the side reactions are less likely to be important.

The large group of six compounds having a nitrogen atom attached to the dimethyl amino ethylene are divided into two groups of three each. The first group has a benzyl radical as part of the large R radical. This benzyl group increases basicity of the large R about 300 times. The three compounds are Pyribenzamine [N (2 pyridyl) N (benzyl) N' N' dimethyl ethylene diamine], Neo-Antergan [N (methoxybenzyl) N (2 pyridyl) N' N' dimethyl ethylene diamine], and Neohetramine [N (methoxybenzyl) N (2 pyridimidyl) N' N' dimethyl ethylene diamine].

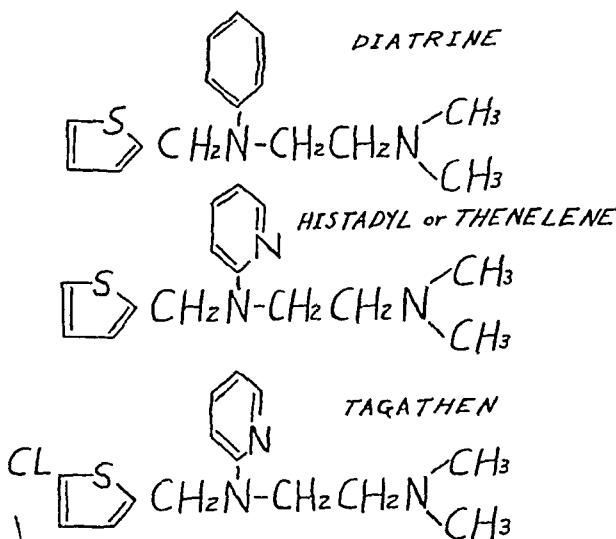
When compared by animal experimentation, the addition of the methoxy group to the benzyl radical markedly improved the antihistaminic activity of the compound. However, clinically there is often little difference between the action of Pyribenzamine and Neo-Antergan.

THE ANTIHISTAMINIC DRUGS—SEYLER

The substitution of the pyridimidyl group for the pyridyl group, as in Neohetramine, reduces the antihistaminic activity on animals but lowers the toxicity also. Clinically this drug is not as potent as the two previous compounds but it also has fewer side reactions.



The second group of compounds having a nitrogen atom attached to the dimethyl amino ethylene has a 2 phenylmethyl group attached as part of the large R radical. Chemically and by animal experiment and clinically this does not appear to make much change in the reactions of the compounds. The three compounds are Diatrine [N (phenyl N (2 phenyl-



methyl) N' N' dimethyl ethylene diamine], Histadyl or Thenylene [N (2 pyridyl N (2 phenylmethyl) N' N' dimethyl ethylene diamine], and Tagathen [N (2 pyridyl) N (2 phenyl 3 Cl methyl) N' N' dimethyl ethylene diamine].

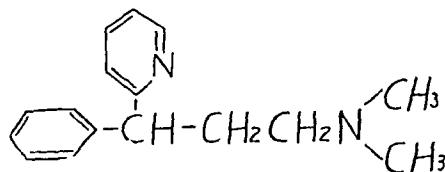
THE ANTIHISTAMINIC DRUGS—SEYLER

The substitution of the 2 pyridyl group for the phenyl group, as in Histadyl, increases the animal-tested antihistaminic activity of the compound and also seems to make it more potent, clinically. However, it also may increase the side reactions.

In Tagathen, the addition of the chlorine radical to the phenyl methyl group doubles the antihistaminic activity of the compound in animal tests. However, in its clinical activity it is very similar to the compounds like it without the chlorine added.

There is only one commercial drug where the large R radical is attached to the Dimethyl amino ethylene by a methyl group. This is Trimeton [1 phenyl 1 (2 pyridyl) 3 dimethyl amino propane].

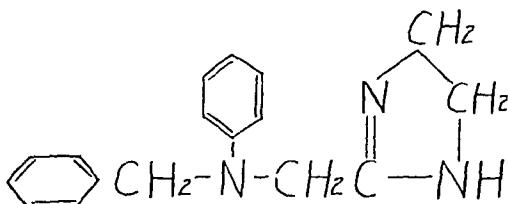
TRIMETON



This compound is not as active by testing on animals or clinically in the role of an antihistaminic as either of the other two groups of compounds with the nitrogen or oxygen attached to the dimethyl amino ethylene. However, it is also neither as toxic nor as likely to cause drowsiness. In fact in some patients it may be stimulating.

One of the oldest antihistaminics that is not nearly as active either on animals or in clinical use is Antistine (2 phenyl, benzyl amino ethyl imidazoline).

ANTISTINE

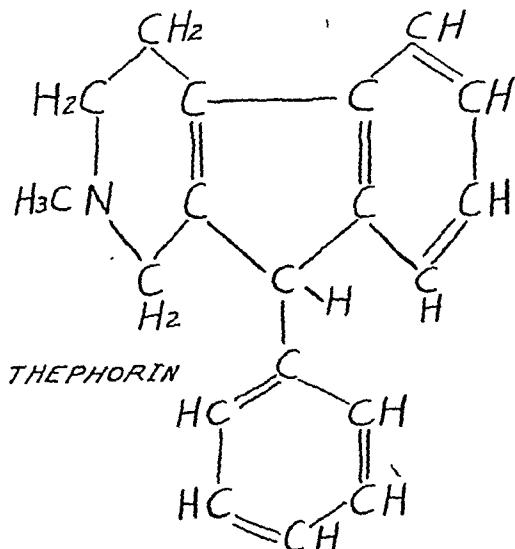


By animal experimentation this compound is very weak compared to all the others. When used clinically, even when used in double the dosage, it does not compare favorably. However, it is not irritating when used locally in the nose or eyes, and for that reason it is at times useful. Its best results, when compared to other drugs, are in the relief of urticaria, where it seems to be quite effective if the dosage is large enough. It produces wakefulness as a rule and not sedation. This compound does not

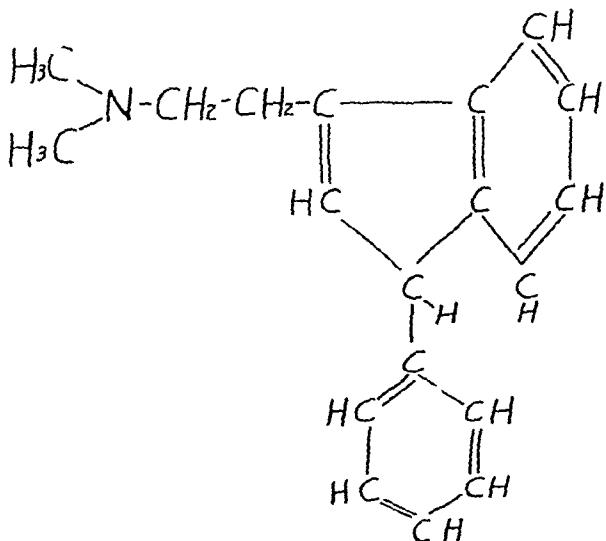
THE ANTIHISTAMINIC DRUGS—SEYLER

contain the dimethyl amino group as such, but probably the imidazoline hydrolyzes to produce it in the tissues.

The last of the commercially available antihistaminics by its structural formula is quite different from the others. It is Thephorin (2 methyl, 9 phenyl, 2, 3, 4, 9 tetrahydro, 1 pyridindine).



It is easy to see how this compound could break down in the tissues to form a dimethyl amino ethylene by breaking the ring where the nitrogen is found. We now have the following compound:



This drug is as effective by animal experimentation as most of the others. It is also quite useful clinically. The greatest advantage in its use is in those patients in which the other antihistaminics produce drowsiness. This compound's most troublesome side reaction is nervousness.

We thus find that we have available four groups of compounds: first,

THE ANTIHISTAMINIC DRUGS—SEYLER

Benadryl, Decapryn and Hydrillin; second, Pyribenzamine, Neo-Antergan and Neohetramine; third, their close relatives, Diatrine, Histadyl or Thenylene, and Chlorathen; and fourth, the miscellaneous group, Trimeton, Antistine and Thephorin. By an understanding of the relationship by chemical formula of these compounds we can use them more intelligently. Clinical experience has shown us all that patients not relieved sufficiently by one of them will often receive satisfactory relief from some other one; also, that side reactions that prevent entirely the use of one may be absent or tolerated when another type of drug is used. Therefore they should be tried out by first using one in each group. If relief is obtained but the side reactions are too severe, one should change to another less toxic drug in the same group. If not sufficient benefit is obtained, one can change to another group. The miscellaneous group is especially useful in those patients where the other drugs produce marked drowsiness.

817 Third National Building

CHLOR-TRIMETON IN HAY FEVER

(Continued from Page 321)

drowsy, two of them with the 4 mg., one with the 2 mg. dosage. This represents an incidence of more intense reactions of 1.2 per cent. Eight persons discontinued the drug because of their reactions, an incidence of 2.4 per cent. Of these, six had previously been unable to tolerate other antihistaminics. The other two were able to tolerate alternate drugs. The remaining 324 persons continued the use of the drug. Their toxic symptoms either disappeared after the first day of use of Chlor-Trimeton maleate or were so mild as to be inconsequential. Almost all of the cases in whom drowsiness was experienced had had similar effects from other antihistaminics.

SUMMARY

Chlor-Trimeton maleate is a highly effective therapeutic agent, especially useful for the symptomatic relief of hay fever alone or accompanied by other allergic manifestations. It is effective in a dose of 2 to 4 mg. three times daily. Results with the smaller dose appear to be adequate in about half of the cases. Chlor-Trimeton maleate possesses an extremely low toxicity and is likely to cause no more than 3 per cent severe side reactions.

170 Maple Avenue

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DENERVATION OF THE LUNGS FOR BRONCHIAL ASTHMA

Case Report

MORRIS W. SELMAN, M.D.
Toledo, Ohio

SURGERY is finding a place in the treatment of severe cases of intractable bronchial asthma. There is enough experimental and clinical evidence to show that removal of the nerve supply to the lung has a sound basis in the treatment of bronchial asthma.

In 1929, Phillips and Scott wrote a comprehensive paper on the surgical treatment of bronchial asthma. They discussed the rationale of this treatment and the various surgical procedures that had been used.

In 1942, Rhienhoff and Gay reported a total of twenty-one cases treated by bilateral resection of the posterior pulmonary plexus. The operation consisted of exposing the vagus nerve through an intrathoracic approach and cutting all the fibers to the lung. In addition, the areolar tissue of the hilus was cleaned off the bronchus and the pulmonary vessels in order to remove all nerve fibers entering the lung. Of this group, eight patients were dramatically relieved of the asthma.

In 1948, Carr and Chandler reported the treatment of intractable asthma by doing a bilateral dorsal sympathetic ganglionectomy. They reported five patients treated by this method whom they had observed from four to ten years. All of these patients, who had been totally incapacitated, obtained enough relief to be able to return to work.

In July, 1948, Brian Blades reported four cases of intractable asthma relieved by unilateral denervation of the lung. The operation consisted of a transthoracic resection of the branches of the vagus nerve to the lung and the removal of the areolar tissue around the hilus of the lung. He cleaned as much of the tissue as possible off the pulmonary vessels and bronchus in order to destroy any invisible fibers entering the lung. He chose the left side because of the greater abundance of autonomic nerves on the arterial side of the chest.

Two types of operations are described in these reports. In one operation, the upper dorsal sympathetic ganglia are removed extrapleurally on both sides. In the other operation, the vagus fibers entering the lungs are removed through a transthoracic approach. Anatomic and experimental evidence indicate that resection of the vagus nerve fibers to the lung is the better of the two operations.

A review of the clinical and experimental work on asthma reveals the following points:

1. That the state of asthma is due to spasm of the bronchi, swelling of the bronchial mucosa and an increase in bronchial secretions. Any one or all of these factors may be the cause of the asthma.

DENERVATION OF THE LUNGS—SELMAN

2. That the extrinsic nerve supply of the lung is derived from the sympathetic and vagus nerve fibers. These fibers are arranged about the posterior surface of the hilum of the lung to form the posterior pulmonary plexus.
3. That the normal state of the bronchial tree (tone, bronchial mucosa and secretions) depends on a balance between the sympathetic and vagus nerves to the lung.
4. That both the sympathetics and vagus contain motor and sensory fibers.
5. That the vagus contains mostly bronchoconstrictor fibers, and that the sympathetic system contains mostly bronchodilator fibers.
6. That a reflex arc exists through the sympathetics and vagus. By interrupting the nerve pathway, the asthmatic attack can be prevented. This is the rationale of surgical denervation of the lung.

CASE REPORT

Case 1.—V. M., a white woman, aged thirty-four, developed a severe "chest cold" in the fall of 1943. Along with this cold, she had her first attack of asthma. Ever since then she had asthmatic attacks that increased in duration and frequency. During the past two years she had been in a state of intractable asthma. Her periods of relief from asthma never lasted more than three or four hours. The patient was totally incapacitated because of the asthma. It was practically impossible for her to leave the house. In 1943, a complete examination including skin tests was done by a competent allergist. The only allergy that manifested itself was sensitivity to iodides. The patient failed to improve under treatment. In 1944 she went to Tucson, Arizona, where she remained for three months. She also visited California. However, she experienced no relief in these climates. In 1946 the patient entered a well-known university medical center. Complete studies, including a psychiatric examination, were done. The psychiatric examination failed to reveal any psychogenic basis for the asthma. A final diagnosis of intractable intrinsic asthma was made. Treatment was instituted. However, the patient failed to improve. In 1947 she was treated by a course of deep x-ray therapy over her lungs with no response. All types of medical treatment were tried with no avail. Aminophylline, adrenaline and aerosol penicillin were used frequently. However, the asthma became progressively worse.

Examination in May, 1948, revealed a thin white woman in a state of asthma. Auscultation of the lungs revealed the typical long expiratory wheeze of asthma. The rest of the examination by systems was essentially negative. X-ray of the lungs revealed increased bronchovascular markings in both lung fields. Bronchoscopy on two occasions revealed a hyperemic mucosa and viscid mucoid secretions in both bronchial trees. There was a marked expiratory intrusion of the posterior bronchial wall into the lumen.

On July 21, 1948, a thoractomy was done by resecting the fifth rib on the left side; denervation of the lung was performed. The vagus nerve was exposed by blunt and sharp dissection from the level of the aorta to the diaphragm. The nerve was elevated from its bed and all branches entering the lung were severed between ligatures. There were two branches along the superior aspect of the pulmonary artery. There was another branch originating from the recurrent laryngeal nerve that coursed along the anterior surface of the pulmonary artery. The largest branch that was severed passed along the posterior surface of the main stem bronchus. One branch passed behind the superior pulmonary vein, and two branches were found

DENERVATION OF THE LUNGS—SELMAN

along the under surface of the inferior pulmonary vein. Several minute branches could be seen going into the hilus of the lung. A few other very small branches were severed as they crossed through the posterior mediastinum to the other side. The inferior pulmonary ligament was divided up to the inferior pulmonary vein in order to eliminate any fibers that might be coming from the contralateral side. As much of the tissue as possible was cleaned off of the bronchus and the pulmonary vessels. The mediastinal pleura was then interposed between the nerve and its bed in the mediastinum. The pleural cavity was closed in layers.

The patient's response to this operation was dramatic. She experienced immediate relief of her asthma and remained free of asthma during her entire hospital course. She was discharged on the ninth postoperative day. The patient was free of asthma for one month. However, her attacks started to recur at this time. On September 16, 1948, a denervation of the right lung was performed. Again she was dramatically free of asthma for about one week. However, she continued to have periodic attacks of asthma for another two months which gradually decreased in severity and frequency. During the past three months the patient has been free of asthma. She experiences periodic "choking-up" sensations which are relieved after bringing up secretions from deep in her bronchial tree. Since her last operation she has done things which she had been unable to do for years, such as, lie flat in bed, go shopping downtown, go to the movies and go to a dance. At present she is seeking work as an office stenographer.

NOTE: Twelve months have elapsed since the last operation, and the patient is still free of bronchial asthma.

SUMMARY

1. Anatomic and physiological studies reveal that the extrinsic nerve supply of the lung is derived from the sympathetic and vagus nerves.
2. Clinical and experimental evidence is accumulating to indicate that removal of the nerve supply to the lung has a sound basis in the treatment of intractable bronchial asthma.
3. When all types of standard medical therapy fail in the treatment of bronchial asthma, surgical therapy should be given consideration.
4. A case is presented in which dramatic relief from intractable bronchial asthma was obtained following denervation of the lungs.
5. A final interpretation of the value of denervation of the lungs for asthma cannot be made until further experimental and clinical work has been done.

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2460 Collingwood Avenue

MULTIPLE TESTING BY ELECTROPHORESIS

CHARLES O. MORSE, M.D.,

Palo Alto, California

THE introduction of chemical materials into the skin by means of a galvanic current has been practiced for many years and with many substances.¹

Notably, in the field of allergy, the local administration of histamine and epinephrine by electrophoresis was reported by Abramson in 1938 and 1939.^{2,3,4} In the latter year he reported the introduction of ragweed pollen by electrophoresis for both diagnosis and treatment. In his article Abramson states:

"A new way of studying allergic skin reactions may develop from recent experiments on the electrical introduction of the extracts of ragweed pollen into the human skin. . . . It would be a great advantage in the study of the allergic patient if tests could be made by placing the allergenic material directly on the unbroken skin.

"The advantages of using a method in which the skin is left intact are those connected with the elimination of obscurity produced by tissue injury, and the advisability of having a minute amount of the powerful allergenic material introduced at a very slow rate at the same skin level. It has now been found that active constituents of extracts of ragweed pollen which have been dialyzed to remove substances of low molecular weight can be driven electrically into the skin by the phenomenon of electrophoresis.

"Although the method of eliciting skin reactions to allergens by electrophoresis is still experimental, a rather wide field of investigation is opened up. There are innumerable substances which would be of interest to study: the pollens of the trees, other grasses, dusts and other inhalants, such as danders, perfumes, et cetera, as well as foods. In addition it would be very important to ascertain if certain substances which are used in patch-testing would give accelerated reactions or different reactions if introduced by electrophoresis."

In 1940 Dutton⁵ expanded the method by skin testing with twenty kinds of pollen extracts and with foods, epidermals, and miscellaneous substances. He developed an apparatus with ten positive leads, each with its own milliammeter and rheostat. He stated:

"The skin reactions obtained by this method are quite similar to those obtained by scratch or intradermal testing, with flushing surrounding a definite wheal. Sometimes there are multiple papular points in the center of the reddened area which do not coalesce. In control reactions and negative reactions there is no evidence whatsoever of change in the skin. We have, therefore, been led to adopt the tentative interpretation that reddening without papule or wheal formation is a weak positive reaction. . . . We have come to believe that tests by this method more closely parallel actual clinical sensitivity than do tests by other methods."

Interested in the possibility of dividing the active allergen carrying electrode so that multiple testing might be carried out with a single lead, an apparatus was finally developed which seemed to solve this problem. Th

MULTIPLE TESTING BY ELECTROPHORESIS—MORSE

active electrode consists of a flexible sponge rubber pad; approximately one-half inch thick, in which are imbedded small sockets. These sockets are connected in series by fine, flexible wires. Into these sockets are screwed plastic cups by means of a metallic stud which forms the base of the cup.

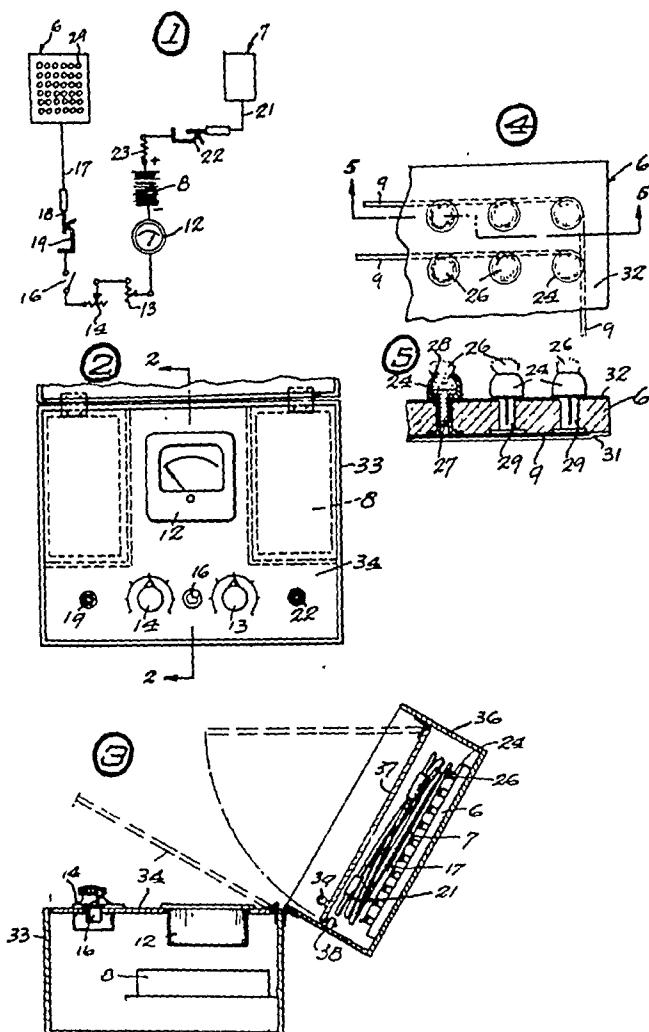


Fig. 1. (1) An electrical wiring diagram of the apparatus. (2) A layout showing the panel arrangement and the controls. (3) A section of the apparatus through line 2-2 of (2). (4) A partial top view of the flexible pad. (5) A section of flexible pad and cups showing cotton balls.

In operation each of the cups contains a small cotton ball which is saturated with an extract to be used in the test, the extract thus coming in contact with the metallic stud. The pad in use by the author at the present time contains sixty-six cups, although any number can be used, each having an effective area of approximately 0.5 square centimeter.

The active electrode is connected to the negative pole of a simple galvanic apparatus, receiving its current from two forty-five volt "B" batteries. The indifferent electrode is a small sheet of zinc which, in use, is wrapped with a wet towel and connected to the positive pole. Suitable rheostats for

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coarse and fine adjustment of the current and a milliammeter complete the apparatus (Figs. 1 and 2).

As Dutton pointed out, "The most important (problem) probably centers around the type of extract to be used. . . . The pH, the presence of

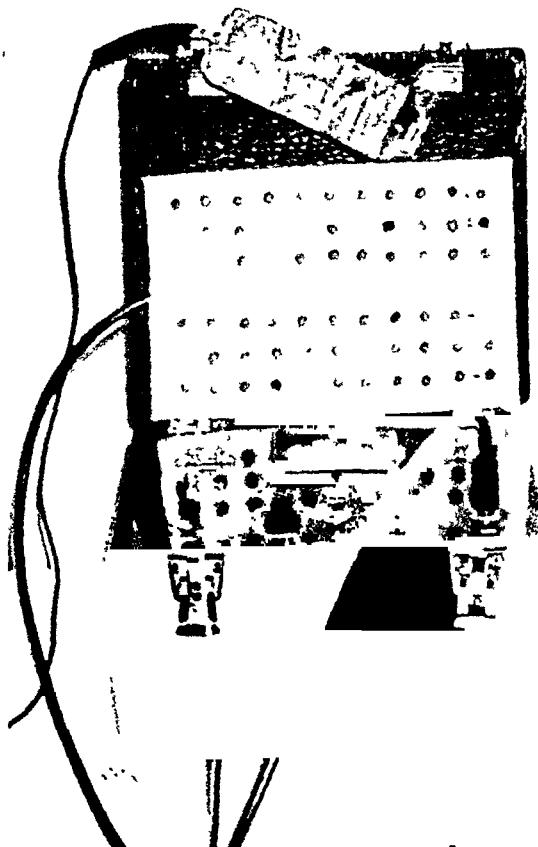


Fig. 2. A photograph of the apparatus.

electrolytes, and the concentration of the substances in solution, all have a highly important bearing on the production of sufficient mobility of the substance to insure that adequate amounts enter the skin." He found that in using aqueous extracts he obtained considerably more penetration, as evidenced by the size of the resulting wheal. My own experiments have borne this out, but in actual testing with pollens glycinerated extracts have proved to be satisfactory.*

In testing practice the patient is placed prone on a table with the back and chest bare. The back is prepared by lightly scrubbing with ether to remove the natural oil from the skin. The indifferent electrode (zinc plate) covered with a wet towel is placed beneath the chest and the lead connected to the positive pole of the apparatus. The flexible pad is placed on the patient's back and held in place by light sand bags. The lead from the pad

*Glycinerated extracts 1:20, prepared by Hollister-Stier Laboratories, are the ones used.

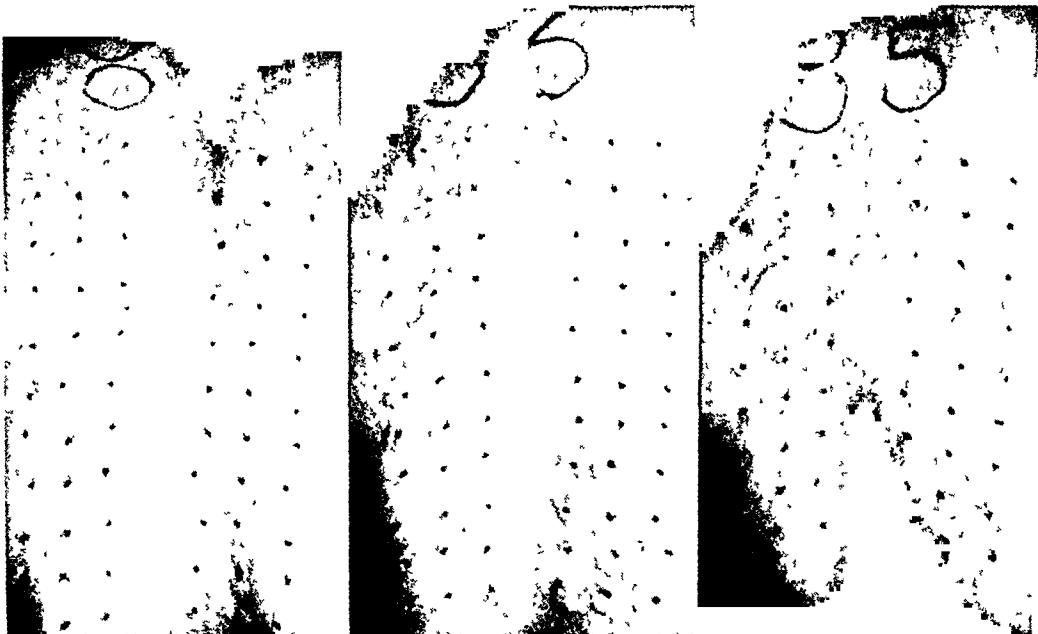


Fig. 3. (left) A photograph of a tested area showing several small reactions. The dark spots in the photographs are ink dots to show the location of the contact points and are not used in routine testing.

Fig. 4. (center) A similar photograph showing many 3-plus and 4-plus reactions.

Fig. 5. (right) A similar photograph showing a very large reaction.

is connected to the negative pole. Care is taken that each of the cups is in contact with the skin. The current is gradually increased to 0.05 milliamperes for each cup in use, or a total of 3.3 milliamperes for sixty-six cups. The pad is left in place with the current on for fifteen minutes. At the end of this time the current is reduced, turned off, and the pad removed. The results of the tests may be read immediately. Positive reactions are such as have been described by Dr. Dutton (Figs. 3, 4 and 5).

For convenience in recording the intensity of the reactions, an area of simple erythema is recorded as 1-plus; small, isolated, papular hives, 2-plus; coalescing hives, 3-plus; a large wheal with pseudopodia, 4-plus.

In operation, the method is entirely without discomfort, the patient experiencing a mild tingling sensation as the current is increased. As the test progresses, the patient often notices itching of various intensity about some of the contact points on the skin.

It has been found that several successive patients may be tested without the further addition of extracts to the cotton-containing cups and that the pad may be stored for several days between tests without the addition of extracts. With reasonable care in placing and removing the pad there is little likelihood of cross-contamination. If cross-contamination has occurred, the cotton balls are removed from the cups, the cups removed from the pad, cleaned, filled with fresh cotton, and moistened with extract. The extract-containing cups are so arranged on the pad that they correspond to a chart listing the allergens in use. This greatly facilitates recording the results. In spite of a large number of pollen extracts applied simultaneously

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and the occurrence of many strongly positive reactions, constitutional reactions have never been observed.

As the method is entirely without discomfort, it is particularly helpful in testing small children. Occasionally, in patients with the dry, atrophic skin of the aged, tests have been negative where intradermal tests were positive.

Positive reactions have been obtained with dust, silk, and other inhalants, and with numerous food extracts, but the author feels that food extracts have not been sufficiently concentrated to give dependable results by this method. Much experimental work remains to be done to realize fully the possibilities of this method.

SUMMARY

1. A brief review of the history of testing by electrophoresis has been given.
2. An apparatus for and technique of multiple testing by electrophoresis has been described.

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261 Hamilton Avenue

Plan now to attend the Seventh Annual Congress of The American College of Allergists February 11-14, 1951, to be held at the Edgewater Beach Hotel, Chicago.

ALLERGY AND THE HEART IN CLINICAL PRACTICE

CLARENCE BERNSTEIN, M.D., F.A.C.A., F.A.A.A., and S. D. KLOTZ, M.D.
Orlando, Florida

HERE are few who debate any longer the question of allergic tissue responses. The works of Rich⁸ and his collaborators, of Criep,¹ Selye,⁹ and others, leave little doubt that cellular injuries may be produced and reproduced in specifically sensitized tissue by the repeated exposure to the specific antigen or hapten, be it food or inhalant, chemical or bacteria. Clinical symptomatology depends and follows upon the site or organ involved in the reaction. The symptoms may be primarily or secondarily the result of the lesion produced. Such lesions may be completely reversible, or lead to necrosis and ultimate cicatrix.³ The cardiovascular system may be the not infrequent major shock organ in such a chain of events. This has been demonstrated by recent experimentations and clinical case reports.^{5,6}

Our attention has been engaged by clinical syndromes involving the heart, either by connotation or by direct reference. The public as well as our profession has been made acutely aware of diseases of the heart and blood vessels, and frequently both patient and physician are led into the too easy assumption that the complaint is a cardiac ailment. We hope to show that much care is needed in confirming many of these diagnoses, and that a high index of suspicion for allergic factors may be the means of avoiding tragic repercussions for the patient and his family, to say nothing of the social and economic importance of the entire problem.

At the outset it must be stated that these cases are not in every instance definitive. The allergic patient grows old and develops the vascular changes of age with all of its implications and accidents. The role of allergic sensitization may be very slight, perhaps the minutest precipitating factor—one difficult to prove. On the other hand we know from the work of Katz⁴ and his group that the coronary circulation goes into spasm on infusion of these vessels with foreign blood. They speculated on the relationship of this phenomenon to the entrance into the human blood stream of foreign proteins which might reproduce the conditions of the experiment. Such spasm was thought to "explain some cases of acute coronary insufficiency and angina pectoris, especially if the coronary vessels are already the seat of narrowing in the larger channels. Vasoconstriction affecting the smaller arteries under these circumstances would increase the resistance to flow in the already narrowed coronary bed." Wilcox and Andrus¹¹ had already shown that coronary constriction occurred in the isolated guinea pig heart following the administration of the protein to which the animal had been previously sensitized. These pure laboratory states probably never exist in man, any more than the so-called "heart-lung preparation." However, two cases of aspirin allergy which have come to our attention perhaps

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very nearly approximate a direct action on the heart, although there were other extracardiac effects. In each instance there were striking immediate conduction and rhythm changes, and in one a coronary occlusion with myocardial infarction from which a rapid and complete recovery ensued.

Quintero and Feros⁷ studied electrocardiogastrographic changes in allergic reactions considered principally to involve the stomach. They demonstrated galvanometric changes due to milk, chicken, potato, and egg in specifically sensitive patients. Histamine likewise was shown to produce significant alterations in the base-line curve. Zivitz and Oshlag¹² report the case of an allergic subject with eosinophilic pleural effusion and pericarditis with effusion which they considered allergic in origin even though they did not feel they had adequate substantiation. Instances of allergic reactions affecting the cardiovascular apparatus abound in the literature,¹⁰ and further interest in the subject has been aroused in connection with the "alarm" reaction of Selye.⁹

The *indirect* effects are so devious as to merit more lengthy discussion. The association of gaseous indigestion, swelling of the stomach or other hollow viscera, with heart pain is a commonplace. Its mechanism has been studied in several ways. The experience of Gilbert, Leroy et al² on dogs in which balloon distention of the stomach was produced and correlated with coronary flow showed a reduction in flow following increase of pressure, more marked when the distention involved the cardiac end of the stomach. Functional disorders of the stomach consequent to pylorospasm and gastric distention almost exactly reproduce this experimental condition. These investigators further showed in humans that anoxia produced cardiac pain more readily after feeding than when fasting, and that such effect could be generally prevented by atropine. They felt that the so-called indigestible foods were more apt to produce cardiac symptoms than the less irritating foods.

Yet it is not enough to prescribe digestible foods without being reasonably sure that allergenic foods, if determined at all, are excluded from the diet. Not infrequently such bland foods as milk, eggs and fruit juices act on an individual allergically sensitive to them, as an irritant or an indigestible. The net effect of these on the stomach, once ingested, is the clinical duplication of the experimental work outlined above with a similar adverse reflex action on the heart (Case 1).

Emotional factors affecting visceral tensions are likewise generally accepted as important in precipitating heart symptoms. In some allergic individuals the only subjective effects noted in the earliest or beginning allergic response are heightened nervous and emotional tensions (Case 2). Indeed it is quite likely that vital medullary centers are so involved. In excessive or very heightened responses, syncopal seizures may follow with drop in blood pressure to shock levels. Individuals in the atheromatous age group may then suffer genuine myocardial necrosis due to the ensuing anoxemia, a coronary accident in no wise as serious in import as the so-

called primary coronary thrombosis. We have seen several cases in this category, one in a patient allergic to Roquefort cheese. Serial electrocardiograms showed changes that were "minimal but definite," and quick and uneventful recovery followed.

Heart failure as observed clinically may not always represent the gradual weakening of a damaged or overworked muscle. Frequently this condition is precipitated by the wildest series of extrasystoles and conduction changes (Case 3). Generally accepted cardiac management is promptly instituted in every instance. However, in our experience, those patients who are found to have food allergies recover compensation more quickly on an exclusion type diet (eliminating observed offenders often found to have been a prominent precipitating factor). They can usually be restored to a circulatory status superior to that prior to the failure episode. It has been noted again and again that their resilience is greater, and the recovery prompter and firmer (Cases 4 and 5).

We cannot feel that the criterion of a single food causation need be invoked in this group of cases, nor that the condition need be reproduced by feeding the interdicted food or foods. The complexities of factors in vascular allergic manifestations tend to obscure the cause-and-effect relationships. These have been critically reviewed by Miale,⁶ with the conclusion that a too simple application of Koch's postulates is not valid, much less necessary. The human experiment in clinical practice cannot be laboratory-wise controlled, nor could we risk the reproduction of the acute heart failure episode in most of these cases. The program is simply *one* of the several efforts directed at a *heart-sparing regimen*. One is forced to rely on the hazardous criterion of clinical results.

Children with cardiac murmurs brought to Florida because of persisting symptoms thought to be due to the rheumatic state occasionally continue with these complaints until their true nature is elucidated (Case 6). In this group once the allergic etiology is found and treated, all evidence of the former disabilities may disappear. Some children are put at bed rest for many weeks because of aches and pains in the legs, low grade fever, and a cardiac murmur. Time and salicylates work no cure, and harassed parents and child seek other explanations. These are the patients who similarly reward the curiosity of the allergy-minded physician, and at the same time have removed from themselves a diagnosis of considerably graver prognostic import.

The general concern over substernal and precordial pain emphasizes the need for careful differential diagnosis, especially when there is slight shortness of breath (Case 7). The subasthmatic seizure must be considered if the victim is to avoid being mislabeled a cardiac. The frank outspoken attack of asthma can be recognized by almost any observer. Between normal respiration and full-blown asthmatic breathing there can be every possible gradation of respiratory difficulty or awareness, both subjective and objective. This possibility must be explored in the resolution of any cardiorespiratory complaint that defies definitive diagnosis (Cases 8 and 9).

ALLERGY AND THE HEART—BERNSTEIN AND KLOTZ

CASE REPORTS

Case 1.—Mr. Wm. G., aged sixty-five years, was seen first because of pain in chest radiating down left arm, and shortness of breath. Two nights previously he ate some peanuts, and several hours later developed nausea with stomach-ache. He then suddenly developed severe pain in precordial region running transversely through his chest and into both arms. The pain eased somewhat and he slept fitfully that night.

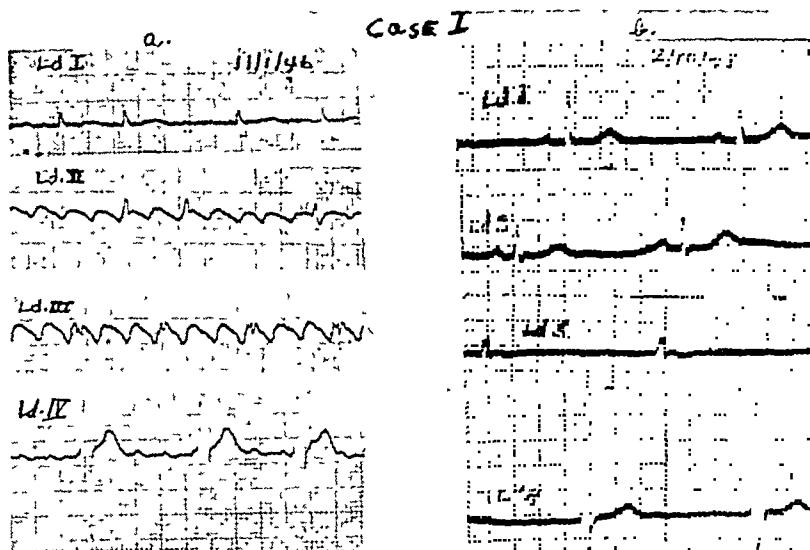


Fig. 1. Case 1. (a) Auricular flutter, varying block. No evidence of posterior coronary thrombosis; proven on serial electrocardiograms. (b) Normal sinus rhythm.

Dull precordial pain persisted the next day, and he noted that his heart seemed to race in irregular fashion. He was seen by his physician that evening and hospitalized because of auricular flutter with possible coronary infarction, posterior in type.

Further history revealed "biliousness" with frequent association of spots before the eyes and dizziness, much bloating and constipation.

It was most difficult to abolish the auricular flutter mechanism, but the patient was clinically relieved and ambulatory following the establishment of A-V block with slowing of cardiac rate to 66 per minute. There was no evidence of coronary thrombosis. In the next few weeks, without change in medications, the A-V block varied with periods of more rapid heart rate following "gaseous" indigestion and food upsets. Many food intolerances were noted, many of which could not be classified in the usual "undigestible" food groupings.

The auricular flutter was eventually abolished and the electrocardiogram revealed a normal tracing with regular sinus rhythm. Two years later patient continues to do very well; he states he is still adhering to allergic food eliminations from diet. He reports that he occasionally gets "spots" before eyes and dizziness and extra heart beats when he becomes careless with his diet in regard to allergies (Fig. 1).

Case 2.—Mr. W. W. L., a retired consulting engineer, aged fifty-eight, had a history of frequent attacks of paroxysmal tachycardia of one year's duration. He had had mild spells of cardiac extrasystoles for forty-two years, but the recent attacks had been incapacitating. Patient had noted that his seizures were always worse with excitement or nervous strain. Hence, his medical treatment had always been directed along these lines employing bromides, phenobarbital and quinidine as necessary. Of

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late he had been forced to cancel several guest speaker commitments because of inability to prevent attacks in spite of medication up to tolerance.

Further history revealed so-called "chronic appendicitis" and "chronic G.B. disease," frequent occipital headaches, chronic sinusitis and laryngitis. Digestive inquiry indicated dysphagia when working hard, occasional heartburn and sour regurgitation one hour after meals. The patient observed food idiosyncrasies to

a. 1/25/47

Case. II b. 3/25/47

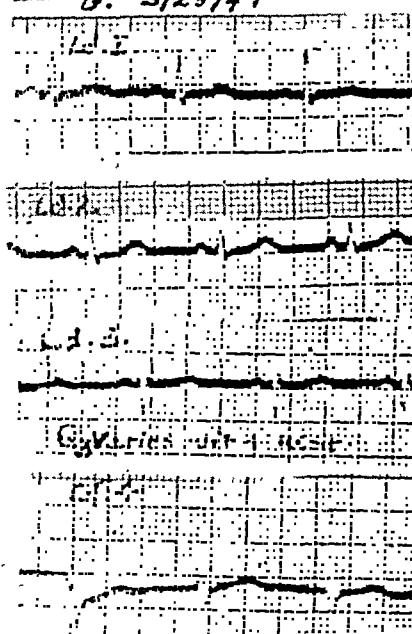
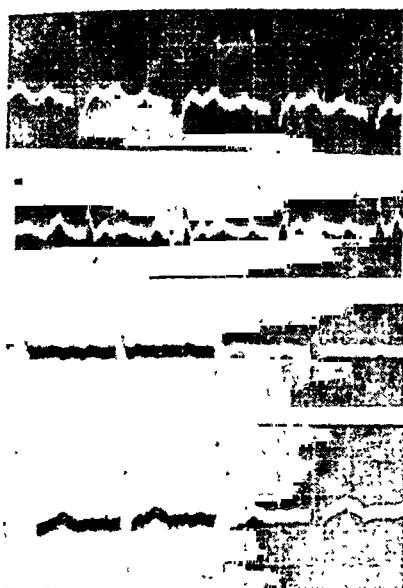


Fig. 2. Case 2. (a) Paroxysmal tachycardia; auricular flutter type. (b) Normal sinus rhythm; no evidence of myocardial damage.

bananas, cheese, tomatoes, chocolate and eggs. At time of examination his cardiovascular status was essentially normal, with regular sinus rhythm, a blood pressure of B.P. 124/70 and normal heart tones. An allergy survey disclosed strikingly positive reactions to several foods, particularly milk and also several inhalants.

Patient was placed on allergic food elimination diet and given antihistamines to be used as necessary for any mild respiratory flare-ups. He declined inhalant desensitization.

His subsequent course has been exceedingly gratifying, except for one attack of paroxysmal tachycardia which occurred following a banquet when he attempted several allergenic foods. Otherwise he has been free of both the extrasystoles and paroxysmal tachycardias. Any increased nervous strain is now more easily controlled by mild sedation. He feels more at ease and less irritable generally, and having a highly developed, inquiring, scientific mind, he wonders why foods had not previously been considered. Incidentally, the one attack of paroxysmal tachycardia for which there was the occasion to treat him, responded most quickly by the addition of castor oil for yielding a more complete and prompt bowel catharsis. Previous attacks frequently required two to three days of complete bed rest and the usual cardiac medications and sedatives (Fig. 2).

Case 3.—Mr. F. H., aged sixty-nine, was admitted to hospital in a semi-comatose state with acute pulmonary edema, pulse rapid and markedly irregular, blood pressure 160/90, heart sounds distant and of poor quality. Patient responded to the

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usual cardiac emergency management after a stormy eight-hour period. The next day his condition improved sufficiently to elicit the history of nocturnal dyspnea of several years' duration, worse in the past two months. He had eaten fried chicken and fried potatoes for the first time in years the evening of the attack. He awakened at 1:00 a.m. with marked abdominal distention and rapidly progressive shortness of breath.

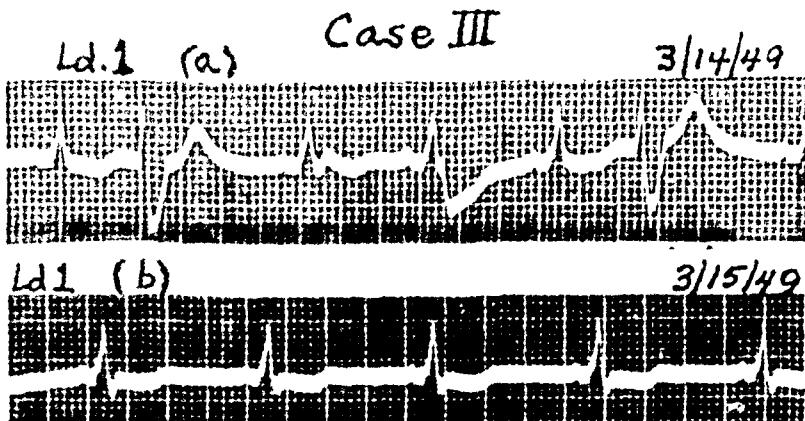


Fig. 3. Case 3. (a) Multiple ventricular extrasystoles. (b) Regular sinus rhythm; digitalis effect.

Further history revealed allergic family background: mother had colitis, and father had asthma. Patient himself had frank asthma at sixteen years of age, with hives, definite food idiosyncrasies to milk, citrus, tomatoes, fried foods and eggs. Proximity to chicken-coop always made his chest tighten up. Skin tests revealed positive reactions to cotton seed oil, citrus, chicken feathers, dust and ragweed.

He was put on allergy exclusion diet and his feather pillow removed. Maintenance doses of digitalis and aminophylline were continued. Within one week the patient felt better than he had in years; lungs were clear; heart sounds were of slightly better quality; there were no extrasystoles and the blood pressure was 100/70; digestion was much improved. He made the trip back North by auto and feels fine. Electrocardiogram taken one and one-half days after attack still showed numerous extrasystoles. Two days later there were no extrasystoles; digitalis effect was noted but no evidence of coronary occlusion (Fig. 3).

Case 4.—Mrs. E. I., aged forty-eight, with known rheumatic heart disease of two years' duration was referred by a cardiologist in her previous residential city. She had a double mitral lesion and aortic insufficiency with auricular fibrillation, and had been in chronic decompensation for at least two years, moderately well helped by salt-poor diet, digitalis and diuretics.

On allergic inquiry it was noted that the patient developed hives from tomatoes and strawberries; citrus and walnuts produced canker sores; milk caused gaseous distention and constipation.

In addition to the cardiac regime, patient was placed on an allergy exclusion diet and antihistaminics when indicated. On this program she felt much improved and for the first time in two years was able to do without an intravenous mercurial injection for five months. At this time she reappeared at the office with the history that she had done well until Christmas when her heart became more rapid without change in digitalis dosage. She developed severe gaseous distention and the chest

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was becoming increasingly congested. Further inquiry revealed that on the day of the onset of the new discomfort patient broke her allergy diet and ate peanuts, chocolate ice cream and cake. She was given castor oil as a laxative, and digitalis dosage temporarily increased. Within two days patient felt fine; pulse rate slowed thirty beats, resuming her usual rate of 68 to 80 per minute.

Case 5.—Mrs. M. P., aged fifty-one, with chronic rheumatic heart disease, had been in decompensation for two years, poorly controlled by the usual cardiac measures, e.g., digitalis, diuretics and salt-poor diet. Further inquiry revealed an allergic family background. Patient also complained of frequent sinus headaches, sneezing spells, constipation, gaseous distention and several known food intolerances.

With the help of food diaries, several skin tests and pulse rate correlations, the patient was able to eliminate several food offenders which had produced headaches, tightening and gaseous distention in the epigastrium. She noted also that several foods increased the heart rate. On the exclusion of the suspected foods the patient had done very well, and the tendency to "breaks" in her heart compensation has been minimized. Recently she returned to the office complaining of daily headaches of one week's duration that were very disturbing to her physical and mental balance. Inquiry revealed no significant change in diet. In view of the fact that the oak pollen season was then at its height, she was tested for oak with other controls. A markedly positive test was obtained, and patient obtained quick relief with antihistaminics, and once again she was spared a possible episode of cardiac decompensation.

Case 6.—T. T., a six and one-half-year-old boy, had recently moved to Florida from Pittsburgh, Pa., on advice of his physician, because of a moderately severe attack of acute rheumatic fever for which he had been hospitalized the previous winter, and the history of frequent upper respiratory infections.

The mother complained that in spite of change of climate the child still had frequent respiratory flare-ups with blocked nose, sore throat and transient swelling and pain in the joints. He had continued to be very nervous, restless, with twitching of fine muscles and an eye tic. Physical examination revealed a fairly well built six-year-old boy, appearing restless and nervous. Nasal turbinates were markedly congested and edematous; uvula was elongated and swollen; pharyngeal wall was slightly reddened with small lymphoid follicles that appeared turgid. Heart revealed no enlargement; a sinus arrhythmia with tachycardia 120 per minute and a definite systolic murmur heard throughout the precordium. Electrocardiogram and blood count were normal, sedimentation rate slightly elevated. It was felt that there were many allergic features present in this case. Allergy survey revealed positive reactions to grass, chicken feathers, house dust, oak, and several foods. He received hyposensitization treatments for the inhalants, and an allergy elimination diet, with excellent results. Six months later he was completely asymptomatic, with normal heart findings, marked improvement of personality and absence of nervous irritability.

Case 7.—A thirty-four-year-old dentist had precordial discomfort amounting to slight heaviness, short of frank pain. A year before he had had a similar experience. He was seen at night because of his feared heart attack. Examination revealed a well-developed male not acutely ill; pulse, blood pressure and cardiac findings were normal. The nasal mucus membranes were turgid, and the breath sounds over the left main bronchus were somewhat harsher than the right. Inquiry revealed that there was a hay-fever history, and that both precordial episodes occurred during the season of grass pollination. An antihistaminic was given and on the following day suspicions of pollinosis were confirmed by brilliantly positive skin tests. The electrocardiogram was entirely normal. The symptoms are due to allergic bronchial ir-

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ritation and spasm, probably resulting in a mild subasthmatic bronchoconstriction with referred pain. Had it been on the right side the physician would not have been called.

Case 8.—A sixty-eight-year-old merchant had complained of loss of appetite and shortness of breath in May. There had been recent noticeable sneezing. He feared heart disease because of shortness of breath the previous August following a Turkish bath, at which time he was told to see a heart specialist. Electrocardiogram was normal at that time and the repeat in May showed no change. He was found positive to grass, ragweed and oak pollens on earlier skin tests. Removal of milk from diet reduced intestinal gas formation. Symptomatic treatment yielded a completely successful outcome and patient one year later has remained free of any so-called cardiac complaint.

Case 9.—A fifty-four-year-old housewife had cough and choking spells for seven years, worse in spring. The year before she was referred by her physician to a heart specialist who proclaimed her normal and offered no therapeutic suggestions. Her mother had also "choked-up," and a sister had frank asthma. The patient could not eat greasy foods and had several food intolerances. Bronchoscopic examination, electrocardiogram, chest x-rays and gastrointestinal series were normal. Skin tests for pollens and a few foods were positive. Early attempts at hyposensitization increased symptoms. Later events proved that the skin was hyposensitive and the patient hyperreactive.

Specific as well as adjunctive therapy has yielded satisfactory results, save for some return of symptoms during sudden seasonal increases in pollen and mold counts.

COMMENT

The evidence cited above is *not* applicable to the *majority* of cases in any one category. It offers nothing new or radical in clinical allergy. It is felt, however, that allergically oriented physicians can do more for many of the so-called cardiac invalids than is offered in routine medical care. Indeed, several pitfalls of diagnosis and therapy may be avoided. In accomplishing this a great weight may be lifted from an otherwise (and unnecessarily), disturbed patient and family, which may at the same time be spared social and economic dislocations of major proportions.

In the development of medicine we have now arrived at the stage where the accurate evaluation of clinical therapeutic results is too frequently said to be invalidated by variable effects on the patient of the personality of the practitioner. Psychogenic factors present in the patient are likewise alleged to detract from the soundness of any definitive conclusions. No doubt both must be borne in mind. However, it is well-nigh impossible to carry into the clinic the rigid controls usually attainable and even mandatory in the laboratory investigation of experimental animals. It simply cannot be done. One must perforce rely on the all too lax and flexible criteria of subjective and objective benefit to the patient, which, fraught as it is with all kinds of error, is after all the ultimate measure of successful clinical therapy.

ALLERGY AND THE HEART—BERNSTEIN AND KLOTZ

SUMMARY AND CONCLUSIONS

1. A group of cases presenting complaints of cardiac origin or implication has been studied. A small but definite proportion of these has been found either on history or physical examination to show evidences of allergy.
2. Such patients when managed allergically may gain prompt dramatic and at times lasting relief from their disabilities. The allergy may be, with rare exceptions, but a contributory cause to the breakdown of an already overburdened individual. This additional therapeutic endeavor is often gratifyingly rewarded.
3. This group may constitute but a small proportion of all cases in these general clinical categories. However, the importance of a possible improvement in the social and economic outlook for these individuals must be constantly borne in mind.

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HAY FEVER IN PALESTINE

Second Report

M. J. GUTMANN, M.D.
Jerusalem, Israel

SINCE the appearance of the "First Report on Hay Fever in Palestine"¹ in 1941, the accumulation of several new facts and experiences indicated the publication of a second report, broadening and rectifying the original thesis. The main correction involves the recognition of the occurrence of hay-fever reactions not only during the spring, as was originally stated, but also during the autumnal season, and in rare cases during the entire year. In describing these changes and new observations, the order of the original paper will be followed.

GEOGRAPHIC AND CLIMATIC CONDITIONS

Although quite naturally the actual climatic conditions of the country have not changed during this short period, the blossoming time of several plants, especially in Jerusalem, has been considerably increased. This has been caused by an improvement in the irrigation and watering facilities. In Jerusalem, for instance, the construction of a water pipeline has led to a longer blossoming season year by year. In the country at large, the increase of land cultivation and the completion of more extensive artificial watering systems, has had the same effect. Then too, this has contributed to the growth of additional and more abundant grasses, shrubs and trees. Originally the heavy khamsins (sirocco) in April and May, with their desiccating easterly winds, had often been enough to end the blossoming season and to dry up the small grasses (relative humidity sometimes decreases almost to zero; values of 5 to 10 per cent are not rare). Now, however, such grasses, through artificial watering, have had their pollinating season extended and intensified. Plants which were formerly considered as rare causes of hay fever now have a much longer season and are of increasing significance. The four to six weeks difference in the blossoming time throughout the country is a result of the wide range of climatic conditions natural in a country which, within a very small area, includes most of the known geographical formations. The spring season blossoming times are approximately as follows:

1. The Jordan Valley from the end of February until the end of March, in watered places until the middle of April.
2. The coastal plain and Esdraelon from the beginning of March until the end of April or from six to seven weeks. Some cases of hay fever are seen until the middle of May, caused mostly by the pollen of Bermuda grass.

I am much indebted to Dr. M. Zohary and Dr. N. Feinbrun of the Department of Botany, Hebrew University, Jerusalem, for their helpful assistance with botanical suggestions and classifications.

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3. The rest of the country, the hill region, from the end of March until the middle or end of May, and sometimes until the middle of June, or from seven to eight weeks or more.

The Haifa Bay, its surroundings and the coastal plain in general have a fall season in September and October. There are many cases of rhinitis and asthma which occur during this period, the causes of which were not clear before the recognition of the autumnal season. This question will be discussed later.

THE CHIEF HAY-FEVER PLANTS OF PALESTINE

In addition to the twenty-two wind-pollinating "plants with practical significance" and the nine non-wind-pollinating "which are deserving of special mention, owing to some particular individual importance," of the first report, we can now list forty-five plants (thirty-three wind-pollinating and twelve non-wind-pollinating).

That these plants do cause hay fever has been verified by direct exposure, positive skin reactions with the pollen extract and successful treatment with pollen extract. Excluded are only *Pinus halepensis* and *Ceratonia siliqua*, since patients gave no response to extracts of their pollen.

HAY-FEVER PLANTS OF PALESTINE*

1. *Acacia farnesiana* (Leguminosae), n, IV-XII. Pollen very toxic for those allergic to it; but since it is not anemophilous, only few are affected.
2. *Agropyron junceum*, Couch grass, coastal plain (Gramineae), IV-V.
3. *Ailanthus glandulosa*, Paradise tree (Simarubaceae), n, IV-V. Cultivated, tree grows rapidly; in recent years, very common here.¹
4. *Amaranthus graecizans*, Tumble weed; *Amaranthus retroflexus*, Redroot pigweed (Amaranthaceae), VI-X. Careless weeds, they shed relatively little pollen.
5. *Ambrosia maritima* (Compositae), V-XI. An exotic species of ragweed, on the coastal plain. Up to the present there has been only one case of hay fever recorded against it. "Even Americans living here who were sensitive to the American ragweeds remain unaffected by the weed."⁴
6. *Andropogon halepensis* (Gramineae), V-XII. Occurs as a weed on irrigated lands throughout the country. *Andropogon hirtus* on rocky ground.
7. *Avena sterilis*, oat (Gramineae) and *Avena baetica*, III-V.
8. *Calycotoma villosa* (Leguminosae), n, II-IV. Occurring especially in the hills.
9. *Casuarina torulosa* and *tenuissima* (Casuarinaceae), VIII-X. Cultivated.
10. *Ceratonia siliqua*, Locust tree or carobtree, St. John's tree, (Leguminosae), n, VIII-XI. General except on higher and cold hills, is alleged to cause hay fever. Patients claim definitely to suffer from sneezing and a nasal discharge when near the plant, especially because of its penetrating odor. Considerations similar to those put forward in connection with citrus blossoms apply here with the difference that citrus odor is quite pleasant. We were unable to obtain positive skin reactions with extracts of this pollen.
11. *Chenopodium murale* (Chenopodiaceae), III-XII. Is present almost throughout the year.

*The months of the blossoming times are designated by the Roman numerals I-XII (January is I, and so forth). All non-wind-pollinating plants are followed by an "n."

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POLLINATION CALENDAR (PALESTINE)

	Jan. I	Feb. II	Mch. III	Apr. IV	May V	June VI	July VII	Aug. VIII	Sept. IX	Oct. X	Nov. XI	Dec. XII
1. <i>Acacia farnesiana</i>				X	X	X	X	X	X	X	X	X
2. <i>Agropyron junceum</i>				X	X	X	X	X	X	X	X	
3. <i>Ailanthus glandulosa</i>				X	X	X	X	X	X	X		
4. <i>Amaranthus spp.*</i>				X	X	X	X	X	X			
5. <i>Ambrosia maritima</i>				X	X	X	X	X	X			
6. <i>Andropogon halepensis</i>				X	X	X	X	X	X			
7. <i>Avena spp.*</i>				X	X	X	X	X	X			
8. <i>Calycotoma villosa</i>				X	X	X	X	X	X			
9. <i>Casuarina spp.*</i>				X	X	X	X	X	X			
10. <i>Ceratonia siliqua</i>				X	X	X	X	X	X			
11. <i>Chenopodium spp.*</i>				X	X	X	X	X	X			
12. <i>Citrus spp.*</i>				X	X	X	X	X	X			
13. <i>Cynodon dactylon</i>				X	X	X	X	X	X			
14. <i>Cyperus papyrus</i>				X	X	X	X	X	X			
15. <i>Echinochloa colonum</i>				X	X	X	X	X	X			
16. <i>Eragrostis cynosuroides</i>				X	X	X	X	X	X			
17. <i>Eucalyptus</i>	X	X	X	X	X	X	X	X	X			
18. <i>Hordeum spp.*</i>				X	X	X	X	X	X			
19. <i>Imperata cylindrica</i>				X	X	X	X	X	X			
20. <i>Inula viscosa</i>				X	X	X	X	X	X			
21. <i>Juncus acutus</i>				X	X	X	X	X	X			
22. <i>Koeleria phleoides</i>				X	X	X	X	X	X			
23. <i>Mercurialis annua</i>	X	X	X	X	X	X	X	X	X			
24. <i>Olea europaea</i>	X	X	X	X	X	X	X	X	X			
25. <i>Panicum repens</i>	X		X	X	X	X	X	X	X			
26. <i>Phleum spp.*</i>				X	X	X	X	X	X			
27. <i>Phragmites communis</i>				X	X	X	X	X	X			
28. <i>Pinus halepensis</i>				X	X	X	X	X	X			
29. <i>Plantago psyllium</i>				X	X	X	X	X	X			
30. <i>Poa spp.*</i>	X	X	X	X	X	X	X	X	X			
31. <i>Polypogon monspeliensis</i>				X	X	X	X	X	X			
32. <i>Ricinus communis</i>				X	X	X	X	X	X			
33. <i>Robinia pseudoacacia</i>				X	X	X	X	X	X			
34. <i>Saccharum aegyptiacum</i>				X	X	X	X	X	X			
35. <i>Salsola herbacea</i>	X			X	X	X	X	X	X			
36. <i>Scirpus littoralis</i>				X	X	X	X	X	X			
37. <i>Sorghum annum</i>				X	X	X	X	X	X			
38. <i>Triticum</i>				X	X	X	X	X	X			
39. <i>Urtica spp.*</i>				X	X	X	X	X	X			
40. <i>Zea mays</i>				X	X	X	X	X	X			
41. <i>Tilia</i>				X	X	X	X	X	X			
42. <i>Jasminum</i>				X	X	X	X	X	X			
43. <i>Syringa vulgaris</i>				X	X	X	X	X	X			
44. <i>Salsola kali</i>				X	X	X	X	X	X			
45. <i>Morus nigra</i>				X	X	X	X	X	X			

*For the species involved see the list of hay-fever plants.

12. *Citrus aurantium*, orange and grapefruit. *Citrus limonium* and *dulcis*, lemon. *Citrus mandarensis*. *Citrus nobilis*, n, III-IV.

Hay fever caused by citrus pollen is rare and occurs only with people working in citrus groves or in their vicinity.⁴ Many people who believe they suffer from citrus blossoms are allergic to *Cynodon dactylon* and other grasses growing in the groves.

13. *Cynodon dactylon*, Bermuda grass, yablith (Hebrew name) or indgil (Arabic). (Gramineae), III-X. Is still the most important cause of hay fever in the country.⁴

14. *Cyperus papyrus* (Cyperaceae), V-X. *Cyperus longus*.

15. *Echinochloa (Panicum) colonum*, purple panic grass, IV-XII.

16. *Eragrostis cynosuroides* (Gramineae), VII-X. Summer blossoming plant, occurs only in the coastal plain from Acre southward.

17. *Eucalyptus rostrata* (Myrtaceae), n, IX-I. Blooming chiefly in the coastal plain.

18. *Hordeum murinum*, barley grass (Gramineae), II-V. *Hordeum vulgare*.

19. *Imperata cylindrica* (Gramineae), III-VI. On the coastal plain and in the upper Jordan Valley.

20. *Inula viscosa* (Compositae), n, VII-XII. In marshes and swampy soil, in the hills. The smell of the leaves is very irritating.

21. *Juncus acutus* (Juncaceae) Great sea-rush, IV-VI.

22. *Koeleria phleoides* (Gramineae), III-IV. Throughout the country, including the desert.

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23. *Mercurialis annua*, Mercury plant (Euphorbiaceae), I-IV. Is spread throughout the country, but not very profusely.
24. *Olea europaea*, Olive, (Oleaceae), n, V. Although it is not wind-pollinating, the pollen is light enough and causes hay fever.
25. *Panicum repens* (Gramineae), IV-I.
26. *Phleum subulatum* (Gramineae), Cat-tail grass, III-IV. *Phleum arenarium* (*Phleum pratense*, Timothy grass does not occur here.)
27. *Phragmites communis* (Gramineae), Common reed, VII-XII.
28. *Pinus halepensis*, Aleppo pine, III-IV. Produces masses of pollen, which seldom cause hay fever.^{2,9}
29. *Plantago psyllium*, plantain (Plantaginaceae), III-IV.
30. *Poa annua*, low spear grass (Gramineae), XII-VI. Grows in irrigated places. *Poa bulbosa*, meadow grass III-IV, *Poa Heckeli* III-IV (Poa *pratensis* does not grow here.)
31. *Polypogon monspeliensis*, Annual beard grass (Gramineae), III-IV. Especially in damp places.
32. *Ricinus communis*. Castor oil plant (Euphorbiaceae), III-IX. It grows chiefly on the coastal plain where it is widespread. Especially III-V.
33. *Robinia pseudacacia* (Leguminosae), n, end of IV-V. Widespread.
34. *Saccharum aegyptiacum* (Gramineae), VIII-I.
35. *Salicornia herbacea*, glasswort (Chenopodiaceae), VIII-XI. In salt places, common.
36. *Scirpus litoralis* (Cyperaceae), V-X.
37. *Sorghum annuum* "durrha" (Gramineae), summer VI-VII. Is domestically cultivated, but only in Arab localities. *Sorghum vulgare*, the chimney millet, "Durrha," is a common weed in Africa.
38. *Triticum vulgare*, wheat cereal (Gramineae), III-V. *Triticum durum* is grown throughout the country.
39. *Urtica urens*, small nettle (Urticaceae), II-IV. *Urtica pilulifera*, Roman nettle.
40. *Zea mays*, corn (Gramineae) summer months, VI-IX (- X). Without great significance because of the high weight of its pollen.
- Occasionally we see a patient with hay fever symptoms derived from:
41. *Tilia*, n, VI-VII.
42. *Jasminum*, n, IV-VIII.
43. *Syringa vulgaris*, lilac, n, IV-V.
44. *Salsola kali*, Russian thistle, IV-V. Coastal plain.
45. *Morus nigra*, black mulberry, III-IV.³

As already mentioned, we observed an additional hay-fever season in autumn in some parts of Palestine. The plants responsible for this hay fever are the following:

<i>Amaranthus graecizans</i>	<i>Cynodon dactylon</i>	<i>Panicum</i>
<i>Amaranthus retroflexus</i>	<i>Cyperus</i>	<i>Phragmites communis</i>
<i>Casuarina ceal</i>	<i>Eragrostis</i>	<i>Saccharum</i>
<i>Ceratonia siliqua</i> , n	<i>Eucalyptus</i>	<i>Salicornia</i>
<i>Chenopodium</i>	<i>Inula viscosa</i> , n	<i>Scirpus</i>
		<i>Zea mays</i>

DISTRIBUTION OF POLLEN-ALLERGY AND ITS CLINICAL SIGNIFICANCE

Although it is impossible to give the exact number of patients, the percentage of hay-fever sufferers in Palestine is approximately the same

HAY FEVER IN PALESTINE—GUTMANN

as in Europe, but is smaller than in North America. This number, however, is considerably greater than is generally assumed by physicians and patients alike. The reason for this is that many cases are not recognized as such and certainly not when they later develop asthma. During the course of systematic allergy testing of asthma patients during summer and autumn, a large number were found sensitive to pollen extracts prepared from the country's pollen. Immediate desensitization brought about quick relief from asthma and, following pre-seasonal or coseasonal treatment with pollen extracts, the asthmatic condition did not recur in the following years as before this treatment.

THERAPEUTIC NOTES

Since 1929,⁵ we have been using intracutaneous injections of pollen extracts prepared in accordance with individual susceptibility. It was observed that the intracutaneous treatment requires more injections than the subcutaneous method, and no unpleasant side effects were observed with the intracutaneous treatment.

Good results were obtained with both the perennial and the pre-seasonal treatment. Even after the beginning of the hay-fever season these injections had a surprisingly beneficial effect.^{6,7}

The result of the treatment depends largely on the use of extracts prepared for each patient according to his special allergy to the various pollens. We are not able to confirm the opinion that different kinds of pollen are so related to each other that it makes no difference which are to be used for injections, for example, that the use of fiorin (timothy) extract alone would be sufficient for a successful treatment for hay fever due to grasses (Harley).⁸ Even if the patient proves allergic to timothy, treatment with it alone is not sufficient if he is allergic to other plants at the same time. These questions shall be discussed in detail in another report.

SUMMARY

The following can be stated as a supplement to the "First Report on Hay Fever in Palestine" (1941) :

1. The blossoming periods are longer than previously reported, following the substantial increase in the area of cultivated and irrigated land during recent years, and in Jerusalem following the construction of a new water supply system.
2. In addition to the spring hay fever during March, May, and June, there also occurs an autumnal hay fever during September and October in some parts of the country (coastal plain). Isolated cases have been known to occur practically through the entire year.
3. New hay-fever plants for Palestine are reported, including some effective during the autumn season.

(Continued on Page 381)

THE USE OF A COMBINATION OF TWO ANTIHISTAMINIC DRUGS IN THE TREATMENT OF ALLERGIC VASOMOTOR RHINITIS

CAPT. THEODORE F. HUBBARD, M.C., AUS, and MAJOR ARTHUR J. BERGER,
M.C., AUS

Washington, D. C.

THEPHORIN* (2-methyl-9 phenyl-2, 3, 4, 9-tetrahydro-1-pyridindene hydrogen tartrate) has been shown to differ from the other known antihistaminic compounds in its side effects on humans.^{1,3,4} In contrast to the other antihistaminics, which most commonly produce depression and somnolence, Thephorin has as its most common side reactions stimulation and insomnia.

It seemed possible to combine this drug with one of the other antihistaminics, providing an antagonistic or nullifying effect on the side reactions and securing an additive antihistaminic effect. The drugs used in this investigation were Thephorin and Trimeton** (phenyl (2-pyridyl) (β -N,N-dimethylaminoethyl) methane hydrochloride).

EXPERIMENTAL

Two hundred patients, each having symptomatic vasomotor rhinitis due to ragweed sensitivity, were the subjects for this investigation. The patients were given each of the two drugs separately in doses of 100 mg. per day, and the two drugs together in a total dosage of 200 mg. per day. Each patient received each form of medication for a period of one to three weeks during the 1948 ragweed season. The patients were divided into three equal groups, and each group received the drugs in different sequence in order that none of the groups would be taking the same drug at the same time. This was done to compensate for the changing pollen count and seasonal variation in symptoms.

The patients were seen at least once a week and questioned concerning the effectiveness of the drug in controlling symptoms. If the patients volunteered any information concerning side reactions, as was usually the case if side reactions were present, they were recorded. If the patients did not volunteer information about side reactions, they were questioned briefly for the presence of untoward effects. The grading of the degree of symptomatic relief and severity of side reactions was made as follows:

Degree of symptomatic relief: O, no relief; +, slight, up to 50 per cent relief of symptoms; ++, moderate, from 50 to 90 per cent relief of symptoms; +++, complete relief of symptoms.

Side reactions: O, none; +, mild, or elicitable only on questioning; ++, moderate, of sufficient degree to be annoying, and volunteered by

From Basic Science Department, Army Medical Department Research and Graduate School and Allergy Clinic, Walter Reed General Hospital, Army Medical Center, Washington 12, D. C.

*Thephorin, brand of Phenindamine, was supplied through the courtesy of Hoffmann-LaRoche, Inc., Nutley, New Jersey.

**Trimeton, brand of Prophenpyramine, was supplied through the courtesy of Schering Corporation, Bloomfield, New Jersey.

ALLERGIC VASOMOTOR RHINITIS—HUBBARD AND BERGER

TABLE I. RESULTS OF TREATMENT OF 200 HAYFEVER CASES WITH THEPHORIN; TRIMETON, AND THEPHORIN COMBINED WITH TRIMETON

	Thephorin	Trimeton	Thephorin + Trimeton
Total number of patients getting symptomatic relief from drug	177	175	189
Degree of relief (number of patients):			
+ (slight)	65	62	31
++ (moderate)	90	94	119
+++ (complete)	22	19	39
Total number of patients having side reactions	85	48	86
Severity of reactions (number of patients):			
+ (mild)	53	36	56
++ (moderate)	11	8	26
+++ (severe)	21	4	4

patient without questioning; +++, severe, of such a degree as to require discontinuation of the medication.

At the conclusion of the study the patients were asked to designate the type medication which they preferred and to compare these drugs with other antihistaminics which they had taken previously.

RESULTS

In Table I is listed the number of patients receiving benefit from the two drugs and the combination, and the number of side reactions observed with each.

The number of patients getting relief from the combination of the drugs was significantly greater ($P=<.02$)† than that observed for either of the two drugs administered separately. There was also a significantly greater degree of moderate and complete relief obtained from the combination ($P=<.001$). There was no significant difference in the number of side reactions observed with Thephorin alone and the combination. However, the Thephorin had to be discontinued in twenty-one patients, while only four patients required discontinuation of the combination or the Trimeton. The number of side reactions observed with Trimeton was significantly smaller than that obtained with the other two forms of treatment ($P=<.002$).

Table II shows the frequency distribution of the types of side reactions to the several forms of medication.

There were fifty patients in the group who reacted to Thephorin with excitatory phenomena on doses of 100 mg. per day. When these patients received this dose combined with an equivalent dose of Trimeton, only twenty-one of the fifty patients complained of side reactions ($P=.001$). Of these, ten still complained of nervousness and excitation; ten complained of dizziness, and one complained of constipation. There were seventeen of the 200 patients who reacted with depression and somnolence to Trimeton on doses of 100 mg. per day. When an equivalent amount of

†The data was analyzed by the method of χ^2 . P is the percentage probability of the observed differences occurring by chance; $P = .05$ or less is considered significant.

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TABLE II. TYPE AND FREQUENCY OF SIDE REACTIONS OBSERVED WITH THEPHORIN, TRIMETON, AND THEPHORIN COMBINED WITH TRIMETON

	Nausea	Anorexia	Constipation	Abdominal Pain	Dizziness	Nervousness, Jitteriness, Exhilaration	Insomnia	Drowsiness, Depression	Fever, Flush	Palpitation, Tachycardia	Dryness of Skin	Dryness of Mouth	Headache	Synope
Thephorin (Number of patients having reactions)	24	7	4	4	9	24	37	7	7	4	4	4	4	0
Trimeton (Number of patients having reactions)	7	0	0	0	22	10	0	17	0	0	2	5	0	0
Thephorin + Trimeton (Number of patients having reactions)	21	2	4	2	30	11	9	30	4	2	4	13	4	1

Thephorin was administered simultaneously, eleven of these patients complained of side reactions ($P=.01$) ; seven complained of depression and four complained of dizziness.

From the above two groups there were nine patients who exhibited both a reaction of excitation to Thephorin and a reaction of depression to Trimeton. When the two drugs were given in combination to these patients, all still exhibited side reactions to the medication. Six stated that they were depressed, and three stated that they felt dizzy or intoxicated.

On questioning at the end of the experiment seventy-five of the patients preferred the combination, sixty preferred Trimeton, fifty preferred Thephorin, and fifteen of the patients felt that all were of about equal effectiveness.

One hundred and ten of the 200 patients had also previously taken both Benadryl and Pyribenzamine. Of these patients, 71.5 per cent found one of these three forms of medication superior to either Benadryl or Pyribenzamine ; 28.5 per cent found either Benadryl or Pyribenzamine superior to any of the drugs used in the present study.

DISCUSSION

We have evidence that the combination of the two drugs afforded a greater degree of symptomatic relief than either of the two drugs taken separately, although an effect as good might have been derived from doubling the dose of either of these drugs.^{1,4} Thus, by doubling the dose of either drug we would expect to double the incidence of side reactions. The observed total incidence of side reactions to the combination was not significantly different from that observed with Thephorin, but the incidence of severe reactions was significantly smaller with the combination. Although the incidence of side reactions with the combination was greater than that observed with Trimeton alone, the number of severe reactions observed was the same. Thus, there was antagonism

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in the side reactions of the two drugs, although this antagonism was not complete.

The total dose in the combination was double that of the drugs given separately, which may have given rise to other toxic symptoms beyond the mild stimulation or depression noted at a lower dose range. A better effect might have been observed if we had attempted to balance the dosage of the two drugs in proportion to the magnitude of the stimulation or depression effects of each drug on the individual patient.

SUMMARY AND CONCLUSIONS

Data are presented on the administration of Thephorin, Trimeton, and the two drugs in combination for a period of from one to three weeks each, to 200 patients with allergic vasomotor rhinitis due to ragweed.

The incidence and degree of symptomatic relief was significantly greater with the combined drugs than with either of the drugs administered separately. The incidence of side reactions with the combined drugs was the same as that observed with Thephorin, but greater than that observed with Trimeton, although the number of severe reactions observed with the combination was no greater than observed with Trimeton, and significantly less than observed with Thephorin. Of the patients, 37.5 per cent preferred the combination, 30 per cent preferred Trimeton, 25 per cent preferred Thephorin, and 7.5 per cent found them all of about equal usefulness. It is concluded that there was a definite, though incomplete, antagonism in the side reactions of the two drugs.

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PSYCHOTHERAPY COURSE FOR ALLERGISTS

Dr. Sandor Rado, Clinical Professor of Psychiatry and Director of the Psychoanalytic Clinic for Training and Research, Columbia University, in co-operation with The American College of Allergists, is presenting a Psychotherapy Course for Allergists in New York City. Lectures will be held 9:00 a.m. to 12:30 p.m. and 2:00 p.m. to 5:00 p.m. daily, November 6 through November 10, 1950. Registration fee is \$100. Information is obtainable from Dr. H. A. Abramson, 133 East 58th Street, New York, N. Y.

INHIBITION OF RED CELLS ISOAGGLUTINATION BY ALLERGENIC EXTRACTS—PRELIMINARY REPORT

RUBEN A. BINAGHI, M.D.

Buenos Aires, Argentina

THE house dust antigen prepared according to a method developed by Sutherland³ has the property of inhibiting the isoagglutination of human erythrocytes, as demonstrated by Rimington, Stillwell and Maunsell.²

I found that this property is not restricted to the dust antigen but is common to many other extracts obtained by a similar procedure, all of which exhibit a great biological activity in scratch or intradermal tests.

As no method is available to determine *in vitro* the allergen content of the extracts, it is obvious that this test would be a very convenient one if the inhibitory power is due to the antigen. Up to the present no definite proof of this has been obtained; however, I have found a very close correspondence between the titer of inhibition and the biological activity, and in any case the increase or loss of one of such properties produces a corresponding modification of the other.

EXPERIMENTAL

Preparation of Extracts.—The material is extracted during forty-eight hours in N/100 ammonia. It is not previously defatted except in the case of seeds. The resulting fluid is clarified by paper filtration, sodium benzoate is added (20 gm. per liter) and then HCl 1:5 until blue to Congo red. The precipitate of benzoic acid, that adsorbs the antigenic fraction, is filtered through paper in a Buchner, and dissolved in acetone where the antigen remains insoluble. It is washed with acetone, alcohol and ether. The greyish or brownish powder obtained is dissolved in a mortar in NaOH N/10, then adjusted to pH 7.5 with HCl N/1 and centrifuged. The insoluble is discarded. The dilution used varied between 0.5 and 5 per cent of solids according to the potency of the corresponding material.

The yield of solid "crude antigen" varies widely with different extracts. Approximately the following results were obtained:

0.015 to 0.05%	cow, cat and dog hair; chicken and turkey feathers; jute; house dust; tufts of the seeds of <i>Platanus acerifolia</i> (buttonwood).
0.05 to 0.15%	horse and goat hair; hemp; orris root; tufts of the seeds of <i>Chorisia</i> sp.
0.15 to 0.60%	rabbit hair; goose and duck feathers; sheep wool; linseed; flax; pyrethrum; tobacco; alfalfa hay.
0.60 to 1.2%	cottonseed; silk worm; dust of grain mill.

- As a rule scratch tests were used and the extracts were maintained in the cooler without sterilization. When used for intradermal tests they were diluted 1:1000 and sterilized by Seitz filtration. In a few cases where sterilization has been carried out by heating at 100° C. during thirty minutes, no significant loss of activity was observed.

Dr. Binaghi is Chief of the Laboratories of the National Institute of Allergic Diseases.

INHIBITION OF RED CELLS ISOAGGLUTINATION—BINAGHI

Determination of the Inhibition of Isoagglutination.—One part in volume of the antigen is added to all the tubes of a series containing one part of a suspension of washed red cells (approximately 1:20 in saline), and three parts of saline. To each tube is added five parts of agglutinating sera conveniently diluted, the dilution corresponding to a tube being twice that of the previous one. A parallel control series is made without antigen and with four parts of saline. A, B or AB group erythrocytes can be used.

Tubes are incubated fifteen minutes at 37° C., then centrifuged one minute at 1500 r.p.m., readings being made after not less than fifteen minutes at room temperature, shaking the tubes immediately before observation. The end point is microscopically read. I consider plus-minus agglutination when very few clumps of two to four cells are present, and plus agglutination when there are clumps of more cells. Moving the stage of the microscope and producing a little sliding of the drop, decision can be made between agglutinated and simple contacting cells.

No differences are observed between first incubating the sera and the antigen and then adding the cells, or incubating the cells and the antigen and then adding the agglutinating sera.

DISCUSSION

All the extracts prepared showed appreciable inhibitory activity, diminishing the agglutinating titer of the sera from two to sixteen times in the conditions described. The biological activity was also very high.

The inhibition test is less sensitive than the biological one: extracts that possess a demonstrable inhibitory power can be diluted about ten times and yet be very adequate for scratch testing. In this connection the technique of Sutherland is specially useful since it is very simple and rapid and produces extracts of very high concentration with the additional advantage of getting solids that remain practically unaltered with time.

The house dust antigen described by Boatner and Efron¹ presents equally high inhibitory power.

No experiences have been realized with pollen extracts.

SUMMARY

1. It is demonstrated that allergenic extracts possess the property of inhibiting red cells isoagglutination.
2. In all the cases studied there is a close correspondence between this inhibitory property and the biological activity.
3. It is suggested the possibility of using such test as a method of estimating *in vitro* the potency of allergenic extracts.

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THE TREATMENT OF ACUTE POISON IVY DERMATITIS WITH 3-n-PENTADECYL CATECHOL BY THE INTRADERMAL ROUTE

A Preliminary Report

HARRY KEIL, M.D.

New York City

THE treatment of poison ivy dermatitis resolves itself into two separate problems: first, the prevention of attacks on exposure to the plant; second, the alleviation of the acute attack. This communication is concerned only with the latter phase. The treatment of acute poison ivy dermatitis with plant extracts has been vigorously criticized by Stevens⁵ and, more recently, by Howell.³ These criticisms have emphasized the following points: the variability in the potency of samples of poison ivy extract found on the market; the many untoward reactions encountered and the occasional worsening of the attack; and the failure to influence the clinical course as well as the subjective complaints. Howell, for example, found no difference in the results obtained in twenty-three cases of acute poison ivy dermatitis, which were treated with from one to four intramuscular injections of a plant extract, as compared with seventeen instances of acute poison ivy dermatitis, which were treated with nonspecific measures. The average duration of the course in both groups was thirteen days. It must be stressed that the aforementioned criticisms leveled at parenteral treatment of this affection were concerned only with poison ivy extracts, which are admittedly unstable, cannot be quantitatively standardized by chemical methods, and are not free from extraneous plant substances. Moreover, these extracts have been administered by the intramuscular route, less often subcutaneously.

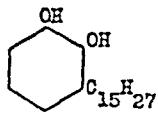
This communication is based on the data derived from the *intradermal* injection of synthetic 3-n-pentadecyl catechol in twenty-seven moderately severe to very severe attacks of poison ivy dermatitis observed in twenty-five patients.* Both the substance used and the method of administration represent a fresh approach to this vexing problem. Although it is difficult at times to assess the value of therapy in this disease, the subjective and objective results obtained in this group of twenty-five severe cases were sufficiently promising to warrant a report at this time.

Patch test studies⁴ have shown that patients sensitive to the poison ivy plant manifest constant group reactions to a proper concentration of synthetic 3-n-pentadecyl catechol (0.1 to 1.0 per cent in any suitable solvent, for example, isoamyl acetate). The active ingredient in the plant causing this dermatitis is a catechol compound with an unsaturated normal side chain of fifteen carbon atoms in the 3-position, the side chain having an

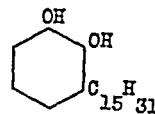
*Drs. R. L. Parker and A. Neumann independently treated sixteen additional cases of poison ivy dermatitis with this method. At least five were severe examples of the disease. Both expressed satisfaction with the results obtained. Dr. Parker used concurrently one of the alcoholic extracts on the market, and he found that "the results were superior" with 3-n-pentadecyl catechol. I have not incorporated these data here since the cases were not under my own direct observation. These additional data offer a rough comparison and substantiation of the results obtained with the material to be reported in this communication.

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average of two double bonds in positions as yet undetermined.² On the other hand, synthetic 3-n-pentadecyl catechol differs from the active ingredient in the poison ivy plant in that the side chain is fully saturated. The following formulas will illustrate this difference.



3-n-pentadecadienyl catechol**
(poison ivy "urushiol")



3-n-pentadecyl
catechol

**The same chemical formula designates the active ingredients in *rhus diversiloba* (poison oak), *rhus venenata* (poison sumac) and *rhus vernicifera* (Japanese and Chinese lac tree).

As stated, the active ingredient in the poison ivy plant is an unsaturated oil which is unstable and cannot as yet be standardized by chemical methods. Contrariwise, 3-n-pentadecyl catechol is a crystalline synthetic substance¹ which is potent, can be standardized quantitatively, is stable in oil solution and is easily handled.

Hitherto, most therapeutic endeavors have been based on intramuscular or subcutaneous injections. It was felt that the chances for a more successful method might be increased by placing the injected solution closer to the site of the "shock organ" in *rhus* dermatitis.

After many preliminary trials with various dilutions,† the most satisfactory concentration for treatment was found to be a dilution of 0.001 per cent 3-n-pentadecyl catechol in sterilized peanut oil. This will be designated as the treatment solution. The dosage of the treatment solution ranged between 0.1 and 0.3 c.c.; the average dose and the optimal one used for the vast majority of cases was 0.2 c.c., which was generally repeated in forty-eight hours. The injection was given into the cutis proper, using a 27-gauge needle, and no attempt was made to raise a wheal. The left arm was injected when the patient was right-handed, and contrariwise, the right arm was used in left-handed people. No other treatment was recommended, and the patients were merely asked to continue, if they wished, any simple bland measure employed prior to observation. In an occasional instance large bullae were drained of fluid when there was mechanical distention in the part.

The side effects encountered with the administration of poison ivy extracts range from local to constitutional exacerbations.³ In contrast, no disturbing reactions were encountered following the intradermal injection of the treatment solution (3-n-pentadecyl catechol in peanut oil) in the dosage used. In occasional instances the site of injection became slightly indurated and pruritic, especially when the solution was placed superficially enough to produce a wheal, but such effects were mild and transient. Focal reactions in areas of eruption were not encountered, although

†Studies carried out with alcoholic solutions of 3-n-pentadecyl catechol were attempted but had to be interrupted owing to the severe pain experienced by patients.

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this is theoretically possible in persons with unusual hypersensitivity. No constitutional manifestations were seen in this group of patients, nor in the course of other studies, and the medicament was well tolerated by all, including children.

RESULTS OF TREATMENT

The principle of control in evaluating the results of poison ivy treatment is most difficult to carry out with scientific precision. For this reason only moderately severe to very severe cases were intentionally selected for study. Twenty-seven such attacks, occurring in twenty-five patients, were available for analysis. These cases may be divided into two groups (A and B), depending on whether or not patch tests were made prior to treatment.

A.—In the first group (thirteen cases) the patients had rhus dermatitis of a few days' duration. They were patch tested with 3-n-pentadecyl catechol dissolved in isoamyl acetate (testing solution).⁵ All were found to be sensitive to the testing solution in either 0.1 per cent or 1.0 per cent or both concentrations. The reading of the tests necessitated a delay of at least forty-eight hours prior to treatment. One of the most striking features following the treatment was the subjective relief of itching, burning or smarting in from two to four days, three days being the average time. The course of the dermatosis in this group was more difficult to evaluate owing to the time element involved. These points are better illustrated in the following case protocols.

Case 1.—A young man had a moderately severe attack of poison ivy dermatitis of a few days' duration. Patch tests with 3-n-pentadecyl catechol gave the following results: 0.1 per cent concentration, a plus-minus reaction in forty-eight hours and a 2-plus reaction in ninety-six hours. He received an intradermal injection of 0.3 c.c. of the treatment solution, with relief of subjective and objective manifestations in three days. Feeling well, he decided, two days later, to clean out the lots adjoining his home. This time he suffered a more severe attack of rhus dermatitis. He was seen two days after the onset of the eruption and immediately received another intradermal injection of 0.3 c.c. of the treatment solution. Again, there was recovery in about three days. In this case, an opportunity was afforded to treat the patient in a second attack, without the delay necessitated by patch testing.

Case 2.—A boy of eight was observed in a moderately severe attack of rhus dermatitis of five days' duration. Patch test with 0.1 per cent 3-n-pentadecyl catechol (in isoamyl acetate) gave a 3-plus reaction in forty-eight hours. He was then given 0.1 c.c. of the treatment solution and was well in two to three days. This may have been the tail end of an attack. However, several months later he returned with a severe attack of poison ivy dermatitis of four days' duration. He was immediately given the same dosage of the treatment solution and this was repeated in forty-eight hours. There was much relief of the severe pruritus in two or three days and the eruption began to fade.

Case 3.—A woman, twenty-seven years old, came in for severe rhus dermatitis confined to the legs. The attack had been present for a few days and the itching was most intense. Patch test with 0.1 per cent 3-n-pentadecyl catechol gave a 2 to 3-plus

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reaction in forty-eight hours, which became 3-plus in ninety-six hours. She was given an intradermal injection of 0.2 c.c. of the treatment solution, with marked relief of the itching and the eruption in a few days.

B.—In order to avoid the delay incidental to patch testing, a group of fourteen cases of typical poison ivy dermatitis (including the second attacks in Cases 1 and 2) were treated immediately when first seen. These cases were intentionally selected because they fulfilled two criteria: first, the attack was severe, with no signs of abatement or relief of itching, burning or smarting; second, the patients were observed relatively early in the course, on the average three to four days, in no case beyond the fifth day. This group of patients received two injections (0.2 c.c.), generally at an interval of forty-eight hours. The results obtained were similar to those seen in the first group in so far as the relief of subjective symptoms was concerned. The edematous element present in many cases required about two to three days to subside, and the entire dermatosis faded about the fifth day of observation. These points are illustrated in the following protocols, which are given in greater detail to show that the patients undoubtedly had suffered from rhus dermatitis.

Case 4.—A middle-aged woman had suffered from many severe attacks of poison ivy dermatitis in the past eight years owing to contact with the plant which flourished on her farm in Connecticut. The average duration of poison ivy dermatitis in prior years had been about ten days, and during this period she suffered considerably from itching and burning. She came under my observation on the third day of another, probably the most severe, attack she had yet had. There were multiple, vesiculo-bullous diffuse lesions in the form of patches on the right forearm, both legs and in the right popliteal space. These areas were oozing intensely and required frequent changes of dressings to minimize contamination of the overlying clothes. The itching, which had been intense, was now replaced by pronounced smarting at the sites of ruptured bullae. She received an intradermal injection of 0.2 c.c. of the treatment solution. When she returned two days later, there was considerable relief of the subjective symptoms of smarting and much improvement in the appearance of the lesions. She received another injection and four days later she stated that in the interim the subjective symptoms had been completely relieved. In addition, the eruption had also practically faded. The patient expressed the opinion that the course of her case had been considerably attenuated.

Case 5.—A boy, nine years old, played ball in the country. In order to retrieve balls that went astray, he had to go into the bushes. A few days later he noted an eruption that spread rapidly. He came under observation four days after the onset, with the clinical picture of a most severe attack of poison ivy dermatitis. There was tremendous edema of the face, with vesiculation, and the eyes were completely closed. Extensive diffuse areas of vesicular eruption were present on the forearms, and there were scattered similar lesions on the chest and lower limbs. Pruritus was intense. He was given an intradermal injection of 0.2 c.c. of the treatment solution. When he returned five days later, he not only felt better subjectively but the eruption had faded, except for some dried crusted lesions on the upper limbs. He was given another injection in the same dosage at the request of the mother. A follow-up nine days later revealed that the eruption had disappeared shortly after the second injection.

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Case 6.—A man, aged forty-one, chopped down weeds in the country. About four days later, an itchy eruption appeared. He was first seen on the third day after the onset of the dermatosis. At this time he had the clinical appearance of a severe attack of poison ivy dermatitis. There were diffuse patches of vesiculation and linear vesicular lesions widespread over the upper and lower limbs, the trunk and on the face. An intradermal injection of 0.2 c.c. of the treatment solution was given. When seen five days later, there was considerable improvement in the subjective and objective signs of the eruption. Another intradermal injection was given in the same dosage, and two days later the eruption had faded.

DISCUSSION

The principle of using control groups in evaluating the effects of therapy in poison ivy dermatitis is subject to many difficulties. For example, it is almost impossible to select cases of comparable intensity and of equal duration. The inclusion of mild instances of this disease may lead to conclusions of relatively less significance. Under these circumstances it was felt that the second group of fourteen attacks of poison ivy dermatitis of severe type and of extensive distribution provided a valid group for the evaluation of treatment. These cases were seen relatively early in the course; the lesions were widespread, oozed profusely and were often bullous in type; and the pruritus, smarting or burning was intense. This was the sort of attack which would have generally lasted at least ten days to two weeks. Indeed, the past experience of several patients in this group confirmed this duration for previous attacks of comparable severity. The average total duration in this group of fourteen treated cases was eight days from the onset of the attack, with a range of from six to ten days. These results may be roughly compared with those reported by Howell,³ who recorded the same average duration of thirteen days in a group of twenty-three cases of acute poison ivy dermatitis treated with intramuscular injections of a plant extract and in a group of seventeen cases treated by nonspecific agents. In the absence of specific information, it is assumed that Howell's group of forty cases were average cases of poison ivy dermatitis, and therefore included both mild and severe examples. In contrast, my data are based on selected cases of moderately severe to very severe instances of the disease. Concerning the group of fourteen severe instances (Group B), the results obtained seemed to indicate a shortening of the clinical course by a few days, but the most striking feature was the relatively rapid amelioration in the subjective symptoms of itching, burning or smarting. In short, these severe attacks seemed to be better tolerated by the patients, and the opportunities for secondary complications were reduced owing to diminution in the subjective symptoms. It should be noted, however, that no effect is to be expected in the event of secondary complications, such as pyoderma and the like.

SUMMARY

Twenty-seven moderately severe to very severe attacks of poison ivy dermatitis, observed in twenty-five patients, were selected for treatment

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with intradermal injections of 3-n-pentadecyl catechol in peanut oil. The results obtained were especially striking in a subgroup of fourteen very severe attacks of the dermatosis. The outstanding feature was the relatively rapid amelioration of subjective symptoms and the probably shortened course of the eruption. 3-n-pentadecyl catechol, the saturated analogue of the active principle of the poison ivy plant, is a synthetic crystalline substance which is stable in oil solution, can be quantitatively administered and is easily handled. The treatment solution containing 0.001 per cent 3-n-pentadecyl catechol in peanut oil, was injected intradermally in a dosage of 0.2 c.c., which was generally repeated two days later. These injections were painless and given closer to the "shock organ" than has been done hitherto. Constitutional or other important side effects were not encountered. The rationale for the use of this substance in the manner described has been briefly discussed, but the mechanism involved is still under consideration.

ACKNOWLEDGMENT

My thanks are due Prof. C. R. Dawson and Dr. D. Wasserman for the supply of 3-n-pentadecyl catechol, and for their continued interest in this investigation.

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PAPERS FOR SEVENTH ANNUAL SESSION, CHICAGO

Members of The American College of Allergists who intend to submit papers for the Seventh Annual Session are reminded that October 15, 1950, is the deadline. Papers are to be submitted in duplicate, accompanied by an abstract of about 250 words, to the Chairman of the Program Committee, Dr. Albert V. Stoesser, 1409 Willow Street, Loring Park, Minneapolis, Minnesota.

A CYTO-HISTOLOGICAL METHOD AS A DIAGNOSTIC AID IN ALLERGIC ANTRAL SINUSITIS

OLF STROMME, M.D.

Lund, Sweden

HERE is a generally growing comprehension of the importance of early recognition of allergic manifestations in the nose and throat. It is desirable to diagnose the allergy at the earliest possible stage, and then treat it as specifically as possible. A thorough diagnostic procedure with allergy in mind is necessary. Otherwise treatment in too many cases will be symptomatic, and only give temporary results. However, it is not to be denied, that diagnostic difficulties with a superimposed infection on allergy—sometimes only a latent or subclinical allergy—may be very great.

Without an improved technique for examination of discharge from the ear, an allergic otitis media may still be troublesome diagnostically to clear up. An allergic rhinitis is usually a clear diagnostic question, if it is not overlooked, but how many allergic antrums are not periodically washed out or even operated upon without a conscious suspicion of a possible allergy.

A valuable aid for diagnosing allergy of the nose is the nasal smear. Eosinophilia of the shock-organ is regarded as significant, and eosinophile cells in the smear or a histologic examination of biopsy material may give the answer.

A histological examination of the mucosa is not practical as a routine method. Examination of the nasal smear is very often a useful method, but is in many cases of limited value.

The main disadvantage of this method is that it cannot give the degree of eosinophilia in per cent. In a smear we too often find the eosinophile cells gathered in lumps in thickened portions of the smear, and from this to get a reliable impression of the real eosinophilia is impossible. If the smear is full of eosinophile cells, it may be of no importance, and the method is good enough, but in the many cases showing only a minor eosinophilia, it is not sufficiently reliable, and in such cases one is unable to tell if a real eosinophilia is present or not. Who is able to tell if there is only the normal amount of eosinophile cells or perhaps 8 per cent or even 12? And the indications for treatment may be dependent on a correct answer on such a question. At least it would be a very good help to have a correct answer.

Another disadvantage with the smear technique is that part of the eosinophile cells very often will undergo traumatic destruction, and the eosinophile red granules may be scattered. This may make an estimation of a possible eosinophilia more than difficult.

From the Ear, Nose and Throat Clinic, Lund, Sweden; chief, Professor G. Dahlman.
Dr. Stromme is now located in Oslo, Norway.

To this was added 1 ml. serum and 2 drops of Duboin's fixative solution (20 ml. saturated sublimate solution, 5 ml. glacial acetic acid, 1 ml. formalin). After careful shaking this suspension was now centrifuged for twenty to thirty minutes at 3500 r.p.m. Then the bottom-cork was removed and the sediment plug, about 0.5 to 1 cm. long, was dropped into 95 per cent alcohol for fixation, and the usual histological treatment

The whole amount was then centrifuged for fifteen minutes at 2500 r.p.m. Then the sediment and lower clear portion of the suspension, totaling 8 ml., was transferred to the pipette-tube. The whole amount was then centrifuged for fifteen minutes at 2500 r.p.m. To get a homogeneous suspension the test-tube was carefully turned for a few minutes in order not to destroy the eosinophilic cells. This "solid" result of an anterol washing was collected in a graded test-tube. To this was added four times the amount of 8.7 per cent saccharose in physiological saline solution (blood-isotone) to get the mucus dissolved. To get a homogeneous suspension (blood-isotone) to get the mucus dissolved. To this was added 2 drops of Duboin's fixation-

METHOD

This "solid" of Silverstolpe has been found most useful for our purposes, and following the method of Silverstolpe to a certain extent we have modified it to serve our special purpose. In our effort to find a reliable method to differentiate the allergic sinusitis from the purely infectious one, we found it practical to examine the result of anterol washings of out-patients at the clinic in the following way.

We wished to use the result of anterol washings with a method which made it possible to determine the eosinophilia of the nasal secretion in percent.

The method is based on centrifugation in a centrifuge tube of

Silverstolpe has advised a method for estimation of tumor-cells in sputum. The method is based on centrifugation in a centrifuge tube of histological treatment, embedding it in paraffin. The narrow-necked special construction, making it easy to remove the sediment for further examination, brings it out through the rubber cork. The top is closed by another rubber cork through which goes a capillary glass tube. Bottom of the centrifuge tube is closed by a rubber cork. The top is bottom of the centrifuge tube is closed by a rubber cork. This "solid" is then examined at a time.

rather heterogeneous material is then examined at a time.

disadvantage added to the other ones, because only a tiny portion of a infection. Using the result of anterol washings for a smear means another may be periodically blocked, or the function of the cilia impaired due to ent as it is on secretion brought out through the osseum. The anterol osseum

In anterol sinusitis the nasal smear technique is still less reliable, dependent

provement in this respect.

The eosin-methylene blue staining advocated by Hansel is a great im-

provement, nucleic and cytoplasm varieties very much different pH.

granules, will often not offer uniform results, as the staining of

polychrome stains, especially if a superimposed acute or chronic infection is present. The

have a varying pH from case to case, different in acute and chronic cases,

The staining technique is another difficulty. The nasal secretion may

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with embedding in paraffin was done. The preparation was cut in the longitudinal direction with the sections 5 microns thick, and these stained with May-Grünwald and Giemsa (Pappenheim). As diluting solution for the Giemsa stain was used phosphate buffer of 6.8 pH.

RESULT

A histological section is obtained with the cells distributed rather evenly over the field of view, in one layer only, each cell distinctly stained. The eosinophile cells appear with the granules intensely red. All other elements are blue.

The leukocytes are as easy to differential count as an ordinary differential blood count.

COMMENT

The advantage of this method compared with the smear technique is obvious concerning exactness of result.

The histological section of the sediment looks like an ordinary tissue section, and every cell can be examined as clearly and distinctly as in a tissue section. In this histological section there are no mucous strings or lumps as in a smear, which too often blur the vision, hamper a distinct staining, and therefore make the examination too difficult and inexact. We get a practically even distribution of cells in the whole field of view. The staining of the smear is often very dependent on the pH of the secretion, a factor of uncertainty and variability. In the histological section, with the method advised, the staining is no problem at all; it is just as clear, distinct and unvariable as in an ordinary tissue section.

The disadvantage of the method is obvious too, and will limit its clinical use. The method is dependent on a laboratory with the necessary histological equipment.

The prehistological procedure can of course be done in any small laboratory equipped with a good centrifuge. The sediment plug can then in alcohol fixation be sent away for histological treatment.

With these clinical advantages and technical disadvantage, the method advised may be a useful diagnostical aid in selected cases.

SUMMARY

A cyto-histological method—based on Silverstolpe's technique for determination of tumor-cells in sputum—is advised to estimate a possible degree of eosinophilia in antral secretion.

The "solid" result of antral washings is homogenized, centrifugated, and the sediment treated histologically with the sections stained after Pappenheim. A 5 micron section shows the cells distributed evenly over the field of view, in one layer only, every cell distinctly stained. The eosinophile cells appear with the granules intensely red. All other elements are blue. The leukocytes are as easy to differential count as in an ordinary differen-

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tial blood count. A comparison between the smear technique and this cyto histological method is given. The exact and reliable result of the method and the technical disadvantage are emphasized.

The method is recommended as a useful diagnostical aid in selected cases.

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ALLERGY TO COLD IN THE RESPIRATORY SYSTEM

Characteristics and Incidence in the Allergic Patient An Experimental Study

ENRIQUE MATHOV, M.D.

Buenos Aires, Argentina

BEFORE Richet's experiments on anaphylaxis and von Pirquet's creation of the word "allergy," both physicians and laymen were aware of the fact that physical agents such as cold, heat, pressure and light could, in certain individuals, give rise to abnormal responses. Salter (1860) described a case of asthma after the application of cold to the feet. Behier (1866), Blachez (1872) and Negel (1884) were the first to describe cases of urticaria to cold.⁵

The considerable impulse given to the study of allergy at the beginning of this century led W. W. Duke to collect, in a remarkable synthesis, all the scattered observations under a common denominator which he entitled "Physical Allergy."^{2,3} This book also presents a large number of cases of specific reaction to cold, heat, pressure and light.

However, the cases of allergy to light were set aside when it was proved that many of the patients had in their blood sensitizing substances of both the porphyrin and other types,⁹ which were the real cause of their photosensitivity. Also, sensitivity to pressure was seen to disappear on several occasions with the mere extraction of a septic focus, the cure of intestinal disorders, et cetera. Instead, attention was concentrated on allergy to cold, particularly after B. T. Horton suggested that many sudden deaths in the bath, swimming pool or river could be due to an anaphylactic shock.⁷

MECHANISM OF ALLERGY TO COLD

When relating his cases, Duke set forth an immunological theory for the purpose of explaining the phenomena. He suggested that the physical stimulus, when acting on the tissues of a hypersensitive individual, gives rise to a new protein possessing specific antigen properties (autogenous antigens). This explanation is supported by S. Karady's experiments,¹¹ as he was able to anaphylactize guinea pigs with their own serum, "cooled" *in vitro* at a temperature of —5° C. Duke's theory appears to be confirmed by Landsteiner and Chase's latest papers in which they claim to have obtained specific anaphylaxis by means of simple chemical substances linked to exogenous or endogenous proteins. In this case the cold either in a direct or indirect form, would play the part of a haptene; consequently it would be a form of autosensitization of patients to their own modified proteins, in the same manner as psoriasis scales,¹⁰ disorders of the ductless glands,¹⁶ or epithelial desquamation.⁶

But immunological investigations show contradictory results. E. Rajka¹³

From the Technical High School of the Ministry of Public Health, National Institute of Allergic Diseases.

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managed to collect only thirty-six cases in the medical literature in which it is claimed that passive transmission of reagins to cold had been achieved; on the other hand, other authors (Jimenez Diaz, et cetera) emphatically state that they have never attained this, and neither have we in a typical case attended at the Instituto Nacional de Enfermedades Alérgicas (National Institute for Allergic Diseases). However, this might be due either to the fact that, because in order to react, the reagins require that the cold should become linked to or modify a skin protein (something which might not occur in all passive receptors), or to the fact that the sensitivity mechanism is not allergic. Urbach¹¹ believes that in many cases the mechanism is parallergic or simply a vasomotor disorder. This view is favored by the fact that, in certain people, the reaction appears when they come into contact with cold air but not with water or ice, and vice versa, or if the cold air is damp and not dry. In either cases the application of warmth immediately cancels the effect of the cold. Moreover, there are patients who react both to warmth and cold. Therefore, T. Lewis¹² believed that urticaria, for instance, is due to the H substance, which is produced by the skin when acetylcholine is freed by the endings of certain cholinergic nerves that he calls *nocifensors*; these nerves can also be excited by several other mechanisms besides the purely allergic one. As for the nature of this H substance, several authors^{1,8} believe it to be histamine.

FORMS OF ALLERGY TO COLD

The best known and most common is urticaria to cold. Urbach and Gottlieb, who made a special study of it, state if a test to cold were carried out on many patients, the doctor would be surprised by the number of them who present urticaria through this means.¹⁵ General phenomena are also mentioned as caused by cold, from hypertension to collapse and even death.⁷ In the digestive system this agent may give rise to edema of the tongue, esophageal spasms, epigastralgia, colic and diarrhea; in the urinary system, to cystitis and nephritis; in the circulatory, to intermittent claudication, coronary stenosis and spasms of the blood vessels.

It is generally accepted that it is in the respiratory system where the cold affects a large number of the patients. All textbooks state that rhinitis, asthma and spasmodic cough can be caused by cold, and in this respect two possibilities are given: that the factor cold might be a releasing cause in an allergic patient, or that it might be itself the producing factor of the allergy, the latter occurrence being the less common of the two. But in the literature in general, the cases of the respiratory system, and also of the circulatory, digestive and urinary ones, are almost purely descriptive and clinical. With the exception of the aforementioned papers by Duke, it is very difficult to find indisputable cases of respiratory disorders released by cold according to an allergic mechanism.

It is because of this that we have planned this paper with the following goal in view:

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TABLE I

No.	Name	Sex	Clinical Symptoms	Main Causes	Sensitivity to Cold	Pre-Test Examination			Post-Test Examination			Eosinophilic Index	Therapeutic Test
						Pulse	Rhinitis	Sibilant Rates	Pulse	Rhinitis	Sibilant Rates		
1	E.C.	F	Rhinitis Asthma Rhin. Rhinitis	Room dust Multiple Milk	- ++	78 80	- + +	- + + +	76 102	- + +	- + + +	0	Negative
2	R.S.	F	Asthma Rhin.	Room dust Catarhal inf.	- -	88 100	- +	- +	88 78	- +	- +	10	Positive
3	N.H.	F	Asthma Rhin.	Room dust Multiple	- -	70	- +	- +	80	- +	- +	9	Positive
4	T.C.	F	Asthma Rhin.	Multiple	- -	76	- +	- +	92	- +	- +	0	—
5	M.C.	M	Asthma Rhin.	Room dust Wheat	- -	100	- +	- +	72	- +	- +	65	Negative
6	F.C.	F	Asthma Rhin.	Room dust Catarhal inf.	- -	86	- +	- +	88	- +	- +	2	Negative
7	C.R.	F	Asthma Rhin.	Multiple	- -	88	- +	- +	80	- +	- +	0	Negative
8	D.C.	M	Asthma Rhin.	Multiple	- -	90	- +	- +	110	- +	- +	0	Negative
9	A.J.	M	Asthma	Room dust Catarhal inf.	- -	90	- +	- +	88	- +	- +	0	Negative
10	D.S.	M	Rhinitis	Multiple	- -	90	- +	- +	98	- +	- +	0	Negative
11	J.M.	F	Rhinitis	Multiple	- -	90	- +	- +	96	- +	- +	0	Negative
12	E.S.	M	Rhinitis	Multiple	- -	90	- +	- +	96	- +	- +	0	Negative
13	M.G.	M	Rhinitis	Multiple	- -	88	- +	- +	98	- +	- +	0	Negative
14	A.M.	M	Rhinitis	Multiple	- -	76	- +	- +	76	- +	- +	0	Negative
15	L.S.	M	Rhinitis	Milk	- -	88	- +	- +	84	- +	- +	0	Negative
16	P.M.	M	Rhinitis	Butt. Choc.	- -	64	- +	- +	65	- +	- +	70	Positive
17	P.M.	M	Rhinitis	Multiple	- -	64	- +	- +	66	- +	- +	4	Negative
18	C.A.C.	F	Rhinitis	Multiple	- -	96	- +	- +	96	- +	- +	0	Negative
19	C.C.P.	M	Rhinitis	Multiple	- -	78	- +	- +	78	- +	- +	0	Negative
20	E.P.	M	Rhinitis	Multiple	- -	84	- +	- +	84	- +	- +	70	—
21	Z.G.T.	M	Asthma Rhin.	Multiple	- -	76	- +	- +	76	- +	- +	0	Negative
22	J.A.S.	M	Rhinitis	Milk	- -	88	- +	- +	80	- +	- +	0	—
23	O.S.N.	M	Pollinosis	Plane trees	- -	72	- +	- +	72	- +	- +	3	Positive
24	N.M.	F	Rhinitis	Multiple	- -	72	- +	- +	70	- +	- +	10	Negative
25	F.M.	M	Rhinitis	Multiple	- -	98	- +	- +	92	- +	- +	4	Positive
26	J.A.	M	Rhinitis	Multiple	- -	76	- +	- +	76	- +	- +	0	Negative
27	J.A.	M	Rhinitis	Multiple	- -	72	- +	- +	72	- +	- +	0	Negative
28	D.N.	M	Urticaria	Pressure	- -	70	- +	- +	70	- +	- +	0	Positive
29	E.D.N.	M	Pollinosis	Composite	- -	68	- +	- +	66	- +	- +	0	—
30	E.K.	F	Pollinosis	Plane trees	- -	71	- +	- +	70	- +	- +	0	Positive
31	I.S.	M	Asthma	Cold	- -	82	- +	- +	80	- +	- +	77	—
32	N.N.	F	Rhinitis	Multiple	- -	66	- +	- +	66	- +	- +	0	Positive
33	J.F.	F	Asthma Rhin.	Catarhal inf.	- -	77	- +	- +	74	- +	- +	0	Negative
34	Z.M.L.	M	Rhinitis	Room dust	- -	80	- +	- +	80	- +	- +	0	Negative
35	A.M.L.	M	Rhinitis	Composite	- -	75	- +	- +	75	- +	- +	0	Positive
36	E.P.	F	Pollinoses	Catarhal inf.	- -	72	- +	- +	74	- +	- +	0	Negative
37	E.P.	F	Rhinitis	Room dust	- -	81	- +	- +	78	- +	- +	0	Positive
38	L.S.	M	Rhinitis	Composite	- -	77	- +	- +	65	- +	- +	0	Negative
39	M.B.	M	Rhinitis	Catarhal inf.	- -	82	- +	- +	65	- +	- +	0	Positive
40	M.J.	F	Rhinitis	Room dust	- -	65	- +	- +	65	- +	- +	0	Negative

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1. Find a practical method for detecting the sensitivity of the respiratory system to the action of cold.
2. Obtain an objective and easily carried-out test which will show the allergic character of the reactions.
3. Investigate the percentage of reactions to cold among a group of allergic patients.

METHODS

Our investigation has been carried out in forty patients with different allergic syndromes—mostly of respiratory character—who attended the “Instituto Nacional de Enfermedades Alérgicas” (National Institute of Allergic Diseases). We endeavored to study them during the remission stages of their symptoms, although this was not possible in some. The pulse and respiratory system of each patient were examined and three smears of nasal mucus were obtained. Immediately after they were asked to place both hands, up to the middle of their forearms, in cold water at a temperature of 0° to 3° C. for ten minutes; this was followed by a new examination and three more nasal mucus smears. The smears were stained with eosin-methylene blue⁴ for the purpose of an eosinophile count; the percentage was calculated in relation to the total of non-eosinophile cells in the smear, whether they were leukocytes or not. The arithmetical difference between the pre-test and the post-test smears was called *eosinophilic index*, setting it arbitrarily as positive when it was higher than 3.

RESULTS

The results of our investigations appear in Table I. Under the heading “Sensitivity to Cold,” + shows the intensity of respiratory symptoms that cold produces usually or occasionally on the patients; – when these symptoms are absent. The same applies to the heading “Rhinitis and Sibilant Rales.” In the column “Therapeutic Test,” we have indicated the results of the ingestion of antihistamine drugs (Benadryl, Antistine or Neo-Antergan, indistinctly). Those who did not make use of them are indicated by a line —.

In Table II we have summarized the principal data.

COMMENTS

Forty per cent of the patients studied by us stated that they suffered from respiratory symptoms through the action of cold (wind, water, sudden drop in temperature); however, only 17.5 per cent showed any symptoms when tested by immersing their hands in water at 0° C. Two alternative reasons can account for this:

1. The method does not reflect faithfully the mechanism that gives rise to the symptoms, in which case the patients should be tested by placing them in a chamber where cold air can be circulated.
2. Those who react to the test are true allergic patients, and the rest

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TABLE II. GENERAL SUMMARY OF TESTS TO COLD

	Totals	Percentages
Number of cases.....	40	
Male	19	
Female	21	
Stated to be sensitive to cold.....	16	40%
Stated to be insensitive to cold.....	24	60%
Showed respiratory symptoms with test to cold.....	7	17.5%
Showed no respiratory symptoms with test to cold.....	33	82.2%
Positive eosinophilic index (<3).....	8	20%
Negative eosinophilic index.....	32	80%
Effect of antihistaminic drugs (therapeutic test) in patients presenting symptoms to cold		
Positive	5	83.3%
Negative	1	16.7%
Data in patients who showed no symptoms to cold		
Positive	5	22.2%
Negative	17	77.3%

would come within the group of the parallergics and of the vasomotor reflexes.

The symptoms of the allergy to cold were asthma, spasmotic cough and rhinitis with abundant hydrorrhoea: these symptoms appeared either at the same time in a patient or separately. There was always a striking parallelism between the reactions to cold and the eosinophilic index. Only in Patient 18, who had shown intense rhinitis with hydrorrhoea, there was not a higher index. On the other hand, Patients 17 and 20 presented no objective symptoms to the test and had an eosinophilic index of 4 and 70, respectively; the last patient stated that she had intense rhinitis when faced with cold wind. Former results show that the eosinophilic index has a twofold value: on the one hand it is an objective examination unaffected by the patients' statements, and on the other it is an indisputable proof that the symptoms appearing through the immersion in water at 0° C. is not a *vasomotor reflex but a true allergic phenomenon*.

All patients with a positive test to cold stated that these symptoms were usual in them.

Our attention was called to the fact that during the remission period hardly ever were we able to find eosinophiles in the nasal mucus of patients manifestly allergic, although the number of these cells increased sometimes by 70 per cent during the attacks of rhinitis and asthma, whether spontaneous or provoked. This finding leads us to recommend most warmly the method of hand immersion in cold water, not only for learning whether the rhinitis is allergic, but also for the purpose of starting the attack with the suspected agent, with eosinophile counts carried out before and after the test. In occupational allergy this investigation has been started already by J. Scheolnicov, and we believe it would be most profitable to extend it to other grounds.

The pulse examination did not prove useful, as many subjects had emotional tachycardia, and the pulse variations were not illustrative. Therapy with antihistamine drugs gave favorable results in nearly all those subjects with a positive test to cold, stopping the symptoms in some and avoiding their onset in others; however, when the cause of the disorders was not due to cold but to other sensitizations in those patients, those drugs were

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unable to prevent the appearance of respiratory symptoms. Among the allergic patients with a negative test to cold, only the 22 per cent were benefited by antihistamine drugs, especially those with pollinosis.

We also wish to point out that Urbach and Gottlieb¹⁵ emphatically state that skin allergy to cold is quite common; however, only one of our patients (who came to our institution with the diagnosis of urticaria to cold) showed signs of skin allergy.

Finally, we shall relate some complementary studies concerning the mechanism of the phenomena observed by us.

Mrs. R. S. said she suffered from asthma every time she washed clothes with cold water. The immersion test was performed and this promptly brought about an intense rhinitis with hydrorrhœa and dyspnea with sibilant râles; this attack disappeared within one minute when her hands were placed in hot water. On another occasion, and without any explanation to her, before starting the experiment we applied a tourniquet on both her arms, above the elbows; no symptoms appeared. Two minutes after releasing the tourniquet, the original symptoms developed once more and were allayed by the immersion of hands in hot water.

On a third occasion, the attack of asthma was completely avoided by applying an intravenous injection of Antistine, a few minutes before starting the test. A few days later the patient was given a subcutaneous injection of 0.5 mg. of histamine phosphate; although it brought about an intense congestion of the head, cephalgia and tachycardia, there was no rhinitis or asthma. This patient, sensitive among other things to room dust, potatoes and wheat, had her allergy to cold under control with Benadryl or Neo-Antergan; however, when she had asthma through another cause —viz., not due to cold—she reacted very little or not at all to antihistamine drugs, although ephedrine and elimination diets were of positive effect.

C. R. (No. 7) showed approximately the same type of symptoms as Mrs. R. S. Patient 16 (Mr. L. S.), besides being sensitive to butter and chocolate, was said to be also affected by cold. Immersion tests of the hands in water at 0° C. brought about an immediate response in the shape of intense rhinitis, hydrorrhœa and an eosinophilic index of 70. The same test was carried out a few days later with a tourniquet round each arm; however, in this case, rhinitis appeared all the same. The injection of histamine phosphate gave rise to a severe congestion of the head, but there was no rhinitis. Later on the allergy to cold was controlled by antihistamine drugs, but the rhinitis due to butter and chocolate only disappeared with an elimination diet.

After a time (it was already summer), both Mrs. R. S. and Mr. L. S. did not show any reaction to the immersion of hands in cold water and their eosinophilic index was 0; it seems as if they had become spontaneously desensitized, at least for the moment.

Based on these three clinical histories, we feel we can state that there is nothing in them which proves that the symptoms are caused by the histamine arising from the tissues of the hands in contact with cold water. Although it is true that the said symptoms improved with the administration of antihistamine drugs, they were not reproduced by an injection of histamine. Besides, though in two cases the symptoms were not elicited when a tourniquet was applied to the arms, the reverse took place in a very definite case.

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On the other hand, the rapid improvement experienced by the first cases when their hands were immersed in hot water, seems to suggest that there is a partial intervention of a vasoconstrictor mechanism, perhaps through a discharge of epinephrine.

SUMMARY AND CONCLUSIONS

The authors studied the allergic manifestations to cold in the respiratory system of forty patients suffering from various clinical allergies.

Forty per cent claimed that the disorders were brought about by getting cold or wet, but only the 17 per cent showed objective symptoms (rhinitis, cough and asthma) with the test of immersion of hands in water at 0° C. during ten minutes.

The eosinophilic index, viz., the difference between the eosinophile content in the nasal mucus before and after the test, proved to be a most reliable and objective guide.

The presence of a large number of eosinophiles in the nasal mucus of patients that reacted to cold, show that the respiratory symptoms are due to a mechanism truly allergic and not to a vasoconstrictor reflex.

Nearly all these patients benefited by the antihistamine therapy, providing they were not experiencing allergic symptoms due to other causes.

Skin manifestations to cold (urticaria) were rare.

This study does not support or deny that histamine or H substance is liberated in the tissues injured by cold.

Although it is supposed that only the 17.5 per cent of the allergic patients are sensitive to cold in a specifically allergic way, it is believed that before the above-stated figure is taken as a definite one, complementary tests should be carried out in chambers where cold air circulates at a certain speed.

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ALLERGY TO COLD AS AN OCCUPATIONAL DISEASE

Clinical and Experimental Study on 100 Workmen in Meat-Packing Factory

ENRIQUE MATHOV, M.D.

Buenos Aires, Argentina

THE studies mentioned in the preceding paper provided us with certain information on the fact that cold is capable of giving rise to allergic reactions in hypersensitive patients. Consequently, we became interested to learn how far the same physical agent is able to produce allergic reactions in patients selected at random. As with the former investigations we were unable to trace, in the available medical literature, a systematic study from the point of view of the allergic reaction to cold in general, but only isolated observations by Duke and to a certain extent by Urbach; however, these only referred to urticaria to cold (see previous article).

Hence the reasons for the present study which we believe has not been undertaken before from an allergic approach.

METHODS

Our investigations were carried out in 100 workmen employed at the Municipal Meat-Packing Factory of the City of Buenos Aires.* These subjects were taken at random from those who work in the freezing chambers (temperatures between -3° and -30°C) from one to six hours, with intervals of rest in between. At first we studied a group of sixty-five workmen (Group A) who had been carrying out their duties in these chambers for the last five to seven years (average 6.3 years); later we studied another group of thirty-five (Group B) who had been at the same task between two and five years (average 3.8 years).

After a short period of questioning to learn their allergic records and the symptoms usually experienced when entering the freezing chamber, each workman had his pulse taken and the blood pressure was registered in many; afterwards an examination of their respiratory system was performed and nasal mucus obtained for smears on a slide. After this the workmen entered the freezing chamber for their usual task; when they left an hour later the same procedure was carried out once more.

Thirty-two of the workmen in Group A stated that they usually experienced various symptoms when entering the chamber; they were given dragées of Neo-Antergan (*N*-*p*-methoxybenzyl-*N*-dimethyl aminoethyl-alpha-aminopiridine) to be taken daily, half an hour before work. A month later they were questioned as to the result. No placebo was given as control.**

*We wish to express our gratitude to Dr. Benigno R. Garat for allowing us to perform the study on behalf of the Instituto Nacional de Enfermedades Alérgicas (National Institute of Allergic Diseases), and to Dr. Francisco Pataro, Director of Technological Medicine of the Ministry of Public Health, who offered us every facility for our purpose. We also wish to acknowledge the co-operation of the authorities of the Municipal Meat-Packing Factory, of the CAP and especially, of the Staff Manager of the latter institution, Sr. Arana.

**We wish to thank the firm Química Rhodia for providing us with the necessary number of dragées of Neo-Antergan.

ALLERGY TO COLD—MATHOV

TABLE I. SUMMARY OF THE EFFECT OF THE FREEZING CHAMBERS ON MEAT-PACKING FACTORY WORKMEN

Group A	Totals	Percentage
Total of workmen.....	65	
Years of work in freezing chambers (average).....	6.3	
With allergic antecedents.....	16	24.5%
Without allergic antecedents.....	49	75.5%
Stated to have symptoms to cold.....	32	49.2%
Stated not to have symptoms to cold.....	33	50.8%
Showed symptoms upon entering the freezing chamber.....	17	26.1%
Showed no symptoms upon entering the freezing chamber.....	48	73.9%
Positive eosinophilic index of the workmen who reacted to cold.....	14	82.4%
Negative eosinophilic index of the workmen who reacted to cold.....	3	17.6%
Response to antihistamine drugs of the workmen who reacted to cold:		
Positive	13	100%
Negative	0	0%
Response to antihistamine drugs of the workmen who did not react to cold:		
Positive	2	20%
Negative	8	80%
Group B		
Total of workmen.....	35	
Years of work in freezing chambers (average).....	3.8	
With allergic antecedents.....	6	17.1%
Stated to have symptoms to cold.....	20	57.1%
Stated not to have symptoms to cold.....	15	42.9%
Showed symptoms upon entering the freezing chamber.....	10	28.5%
Showed no symptoms upon entering the freezing chamber.....	25	71.5%
Positive eosinophilic index of the workmen who reacted to cold.....	8	80%
Negative eosinophilic index of the workmen who reacted to cold.....	2	20%
General Results (Groups A and B)		
Total of workmen.....	100	
Years of work in freezing chambers (average).....	5.3	
With allergic antecedents.....	22	22%
Without allergic antecedents.....	78	78%
Stated to have symptoms to cold.....	52	52%
Stated not to have symptoms to cold.....	48	48%
Showed symptoms upon entering the freezing chamber.....	27	27%
Showed no symptoms upon entering the freezing chamber.....	73	73%
Positive eosinophilic index of the workmen who reacted to cold.....	22	81.4%
Negative eosinophilic index of the workmen who reacted to cold.....	5	18.6%
Positive response to antihistamine drugs of the workmen who reacted to cold.....	13	100%
Negative response to antihistamine drugs of the workmen who reacted to cold.....	0	0%

RESULTS

A general summary of the results will be found in Table I. The column "Allergic Antecedents" contains those such as asthma, rhinitis with sneezing, urticaria and eczema, which the workmen had experienced outside working hours. In the columns "Stated to Have Symptoms to Cold" and "Stated Not to Have Symptoms to Cold" we have indicated whether the workman usually had abnormal symptoms when entering the freezing chamber for his daily work. The column "Eosinophile Index" shows the eosinophilic index obtained according to the method described in the preceding paper. Lastly, under the heading "Response to Antihistaminic Drugs" we have stated the results obtained with Neo-Antergan. Group B has no such column because the dragées were not given to these workmen.

COMMENTS

Of the 100 workmen studied, the 52 per cent stated to experience certain symptoms when entering the freezing chambers. The symptoms were chest oppression and dyspnea, rhinitis with sneezing or hydrorrhœa, weeping, headaches, pains in bones or muscles, and, sometimes, epigastralgia

and cystalgia. These symptoms, which may appear jointly or separately, constitute a true *syndrome of disease by cold*, which may occasionally be seen in some people when merely exposed to a cold environment. On the other hand, we have never seen a single case of urticaria through cold in those workmen.

However, the examination practiced on the workmen revealed that only the 27 per cent of them showed objective symptoms; those who complained of headaches and cystalgias were not included because of the lack of objective symptoms. This percentage of 27 per cent is higher than that found in the group of allergic patients studied in our preceding paper (17.5 per cent). The reason for this may be either that the method of detection has provided a better reproduction of the usual conditions which bring about the symptoms, or that these patients are enduring more severe and repeated exposure to cold than the allergic ones. It is remarkable that among individuals taken at random there has been a similar or even greater number of allergic subjects to cold than among those patients who have a true allergic "diathesis," as it would seem more logical to expect a higher percentage among the latter. Nevertheless, the situation is rather similar to what happens in the serum disease or in cases of allergic reactions to drugs (sulphonamides), where the incidence is not greater among those individuals with allergic antecedents.

It is important to note that all the workmen with allergy to cold showed relatively mild symptoms, which, although troublesome at times, did not prevent them from working. Perhaps there may have been workmen who were more seriously affected with these symptoms, but it is likely that in that case they would have asked to be transferred to other sections.

An interesting fact is that among Group A (6.3 years of work in the meat-packing factory) and Group B (3.8 years) the incidence of affected workmen showed no appreciable difference. No relation was found between the type of symptoms and the lowest temperatures; on the contrary there was found a large proportion of workmen with symptoms among those who labored in atmospheres not so cold (-3° C.). Perhaps the only visible difference between Groups A and B is that among the latter the symptoms appear to be milder.

Examination of the pulse and blood pressure offered no interesting results. On the whole there was a decrease of both after the test, but this we believe was due to psychological reasons. The eosinophilic index was positive in the 81.4 per cent of the patients who felt symptoms in the freezing chamber. Instead it was always 0 in those who felt nothing; however, in one case of this type, eosinophiles were found in the smear. Lastly, thirteen of the seventeen patients who showed allergy to cold, took "Neo-Antergan." The 100 per cent felt an improvement, either moderate or marked. These were asked to attend the Instituto Nacional de Enfermedades Alérgicas (National Institute for Allergic Diseases) for the purpose of trying out a final course of treatment (histamine, histamineazo-

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protein, progressive cold). Of the remaining workmen who had stated they experience symptoms in the chambers but without objective prove, two out of ten claimed a mild improvement with the therapy. We believe that most of these are not allergic to cold.

SUMMARY AND CONCLUSIONS

Fifty-two per cent of people who work daily in freezing chambers (at temperatures of -3° to -30° C.) stated to experience various symptoms when entering them (rhinitis, asthma, headaches, weeping and cystalgia); however, this was only detected objectively in the 27 per cent.

The symptoms were, in general, of moderate or mild intensity; they did not prevent the people from working, although at times they were of troublesome character. The symptoms appeared in individuals both with and without an allergic record; in those who had worked for the last six years, and those who had done so for only three, and in workmen who labored at -14° C. and also in those at -3° C.

The positive eosinophilic index was associated to allergy symptoms in the 81.4 per cent, and was negative in all the other patients.

The symptoms of the 100 per cent of workmen with allergy to cold improved partially or wholly with antihistamine drugs.

Allergists will be interested in new, versatile photomicrographic apparatus, designed also to serve other aspects of scientific photography. Known as the Orthophot, it provides facilities for photomicrography; photomacrography; micro-projection; laboratory, clinical, and general photography; photocopying; microfilming, X-ray photocopying; and photoenlarging. The apparatus is used with any standard microscope and consists of three basic units easily assembled for any use desired. The reflex camera itself is detachable and can be used on a standard tripod or hand-held for all forms of scientific or general photography. Those allergists who are interested in photography can obtain further information from Silge & Kulme, Box AG, 153 Kearny Street, San Francisco 8, California.

A HEMORRHAGIC BULLOUS ERUPTION DUE TO PENICILLIN G

Relationship Between Chemical Structure and Sensitizing Capacity of Penicillin G and Penicillin O

M. H. SAMITZ, M.D., PETER HORVATH, M.D., and SAMUEL BELLET, M.D.
Philadelphia, Pennsylvania

THE number of reports of serious reactions caused by penicillin sensitivity are becoming more frequent; however, as far as we are aware, no instance of a hemorrhagic bullous eruption has been reported in the literature.² Since the commonly used penicillin at present consists of penicillin G, it would seem feasible that a slight alteration in the chemical structure of penicillin may result in another penicillin which would exhibit antibacterial activity similar to penicillin G, without provoking a penicillin reaction in those individuals who are sensitive to penicillin G. The following case report deals with the clinical employment of such a penicillin:

M. C., a man, aged forty-four, was admitted on June 22, 1948, on the medical service at the Graduate Hospital with the chief complaint of pain in the legs, fever and general weakness. The past history included a "heart attack" three years ago and also one year ago. These attacks were characterized by sudden pain in the precordium following exertion. The pain lasted for one-half hour and did not disturb him unduly. There was no history of rheumatism, scarlet fever or chorea. About two months prior to admission, the patient began to notice pain in the legs which gradually became worse. Three weeks prior to admission he had to stop work. Accompanying the pain was generalized weakness. Two days before hospitalization the left ankle began to swell. There had been a weight loss of eighteen pounds in the past six weeks.

Examination revealed no dyspnea or cyanosis at rest. The heart was enlarged in the transverse diameter, particularly to the left. A rather rough, grating systolic murmur was audible at the apex (Grade III) and at the aortic area. The second sound was absent at the aortic area. The blood pressure was 105/40. The rhythm was regular. The lungs were clear. The liver was enlarged three finger-breadths below the costal margin, the spleen was palpable about two finger-breadths below the costal margin. No congestive phenomena were present. The temperature on admission was 100.2°, pulse 105, and respiration 24 per minute.

Roentgen examination of the chest showed generalized cardiac enlargement especially involving the left ventricle. The remainder of the examination of the chest was negative. Electrocardiogram on June 23 revealed evidence of myocardial damage and left ventricular hypertrophy.

The blood count showed a moderate anemia: red cells, 3,030,000; hemoglobin, 48 per cent; white cells, 7,100; 78 per cent neutrophiles, 20 per cent lymphocytes, 1 per cent monocytes. Except for a faint trace of albumin the urine was negative. Four blood cultures were consistently negative for streptococcus viridans.

The diagnosis in this case was rheumatic heart disease, cardiac enlargement, aortic stenosis, mitral insufficiency, probable subacute bacterial endocarditis. In view of the continued fever and the clinical findings in spite of negative blood cultures, a proxi-

Dr. Samitz is assistant professor of dermatology and syphilology, Graduate School of Medicine, University of Pennsylvania, Graduate Hospital.

Dr. Horvath is a fellow in dermatology, University of Pennsylvania, Graduate Hospital.

Dr. Bellet is assistant professor of cardiology, Graduate School of Medicine, University of Pennsylvania, Graduate Hospital.

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original complaints associated with an elevated temperature. It was suggested that he be readmitted to the hospital to undergo a further course of the antibiotic, a penicillin which was allegedly free of allergic manifestations (penicillin O).*

The clinical findings were identical with those observed on the previous admission. The cardiac findings were similar to those mentioned above. However, his temperature on admission was 103° rectally, pulse 120, respirations 28 per minute. He was started on penicillin O, 100,000 units every three hours. His rectal temperature became normal after eight days and he felt well. On the sixteenth day he was noted suddenly to get into bed because he did not feel well, and shortly thereafter began to sweat profusely, vomited, and developed a left seventh nerve palsy, left hemiplegia, and dysarthria. In fifteen minutes he was comatose, with signs of decerebration rigidity, ankle and patella tonus, Babinski's and Hoffman's signs. The blood pressure was 230/70 (normally the blood pressure was 150/70).

Lumbar puncture revealed a spinal fluid pressure of over 500 mm. water; the fluid was grossly bloody. Three hours later he developed respiratory arrest and was put in an Emerson respirator with an endotracheal tube in place. His temperature started to rise. Nine hours after onset he died with a temperature of 108°.

Autopsy revealed a small pericardial effusion, moderate cardiac hypertrophy, moderate grade of aortic stenosis, and subacute bacterial endocarditis involving the aortic and mitral valves. These valves manifested vegetative and ulcerative lesions. Numerous emboli were observed in the spleen and kidneys. Rupture of a mycotic aneurysm of the right meningo striate artery, resulting in massive cerebral hemorrhage, was probably the immediate cause of death.

CONCLUSIONS

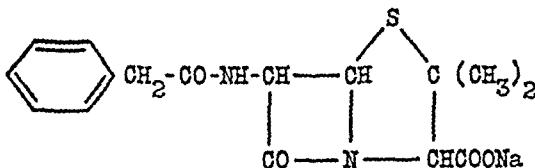
Hemorrhagic bullae have not been included among the drug eruptions caused by penicillin.² Inasmuch as this individual was shown to have subacute bacterial endocarditis, which itself produces hemorrhagic phenomena, it seems possible that these hemorrhagic phenomena combined with the manifestations of a severe penicillin sensitivity to produce the clinical picture shown by the patient.

Various tests are available for evaluation of sensitivity to penicillin.^{1,3} Unfortunately, no definite conclusion can be drawn from the results of such tests,^{3,5,6} and occasionally, promiscuous testing may be dangerous and incapacitating for the patient.⁷ The most reliable method is the readministration of the penicillin in question, and the observation of the patient's clinical course following this test dose. However, such a procedure was absolutely contraindicated in view of the severity of the previous cutaneous picture. The other reliable test to ascertain drug sensitivity is cessation of the suspicious drug, and if involution of the lesions occurs, it is presumptive evidence that that drug was the allergen. This criterion was satisfied in this patient. In addition, in this case the positive reaction to the Urbach-Koenigstein test was suggestive of sensitivity to penicillin G, while no reaction to the administration of penicillin O over a period of 16 days seems to indicate that this patient did not possess any sensitivity to penicillin O. Penicillin O differs from penicillin G in that the benzene ring of the latter has been replaced by the allylmercapto group.¹ In two

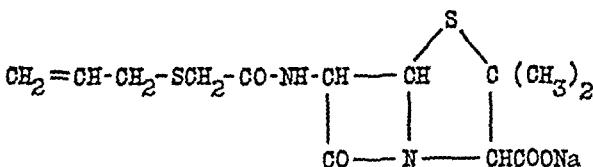
*Material supplied by the Upjohn Company, Kalamazoo, Mich.

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other patients encouraging results were obtained with this new compound when it was used to replace penicillin G which had previously sensitized the patients.



Penicillin G, Sodium Salt (benzyl penicillin)



Penicillin O, Sodium Salt (allylmercapto methyl penicillin)

COMMENT

This patient in whom subacute bacterial endocarditis was suspected clinically, and later confirmed by necropsy, received routine treatment with penicillin G. Although the patient responded well to the treatment, penicillin administration was stopped before the course had been completed because of the development of a severe type of bullous eruption, which was due to his sensitivity to the penicillin. In the experience of one of us (S.B.), patients with aortic stenosis respond somewhat better than the average patient with subacute bacterial endocarditis to penicillin. In this patient, because of the inadequate course of therapy, incomplete healing occurred and the endocardial lesions continued to progress, resulting in death due to the usual embolic complications occurring in such patients. Although he was later started on penicillin O and tolerated this preparation without untoward effects, his condition had progressed to such a degree during the interval period where no treatment was given that he succumbed to the complications of the disease.

SUMMARY

The history of a patient with subacute bacterial endocarditis is reported who developed severe hemorrhagic bullous lesions during the course of penicillin therapy. Because of this complication penicillin was discontinued and the bullous lesions gradually disappeared. Due to the inadequate course of therapy, the infectious process progressed leading to death of the patient. This patient was later able to tolerate penicillin O without the development of allergic manifestations. This preparation was started sixteen days before death but was apparently unable to control the pro-

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gression of the cardiac lesions, probably because of the long interval period during which the patient received no therapy.

In the presence of marked sensitivity to penicillin G, the use of penicillin O, because of the greatly lower incidence of allergic manifestations, may be administered and its use may be life-saving to the patient.

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HAY FEVER IN PALESTINE

(Continued from Page 349)

4. The number of hay-fever sufferers is far greater than previously indicated. Special attention is drawn to the clinically important observation that pollen was found to be the cause of asthma which recurred regularly each year in summer and autumn. Specific pollen treatment eliminated those symptoms.

5. The therapy which has been used by the author since 1929 consists of intracutaneous injections of pollen extracts prepared specifically for each patient. General mixed pollen extracts were less effective.

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AN INVESTIGATION OF THE ROLE OF FUNGI IN WITH BRONCHIAL ASTHMA AND ANTHRACOSIS

J. W. PIEKARSKI, M.D., F.A.C.A.
Wilkes-Barre, Pennsylvania

FORTY-SEVEN anthracite coal miners, who appeared for treatment in the allergic clinic and the medical wards* with complaints of various respiratory ailments associated with dyspnea, furnished the material for this study.

Since such workers suffer frequently from paroxysmal dyspnea characteristic of a bronchial asthma-like syndrome, an attempt was made to learn if these complaints might be due to certain occupational allergens, particularly fungi. A search was also made for individuals who were said to suffer from sneezing and lacrimation when exposed to certain sections of the coal mines.

Authoritative opinion indicated such underground locations satisfy the natural requirements for the growth of these organisms.

Later investigations have shown that the air of certain coal mines does contain large numbers of spores of *Penicillium (Pac) Zaleskii*** and a smaller number of spores of *Stysanus Stemonitis (Pers) Corda*. The fungi form a coat of mycelium several inches in thickness on the various types of timber used.

The following work was based on the concept of Courtright and Hurwitz† (1942-43), who confirmed Ratner's previous success in sensitizing guinea pigs to dry horse dander by inhalation. The fundamental principles underlying this observation are given by these workers as follows: "We agree that the inhalant method of sensitization approaches more closely natural sensitization of man than any other method.

"1. The allergen must enter the body through nasal or respiratory membrane or be held there.

"2. Sensitization is built up by repeated exposures which approximate more closely clinical sensitization.

"3. The respiratory mucous membranes, because of repeated exposure, may acquire resistance to general sensitization, which may not result from the subcutaneous or intraperitoneal routes."

In attempting to clarify the possible influence of atopic or acquired allergy arising from the aerial molds in the coal mines, the following study was undertaken.

A culture was obtained by exposing sterile Sabouraud's media petri

Presented at the Fifth Annual Meeting of The American College of Allergists, April 14-17, 1949, Chicago, Illinois.

*The majority of these patients were subjects of a medical ward and allergy clinic of a general hospital situated in the heart of the anthracite coal region.

**Personal communication with Dr. Carroll W. Dodge, mycologist, Missouri Botanical Gardens, St. Louis, Mo., May 14, 1943. A tentative identification of the mold was made as *Penicillium (Pacekii) Zaleskii*. Reference: Thom: The Penicillia, p. 202.

†L. J. Courtright, S. H. Hurwitz, and Abbie Betz Courtright: Inhalant sensitization of guinea pigs under controlled atmospheric conditions. *J. Allergy*, 13:271, 1942.

ROLE OF FUNGI—PIEKARSKI

TABLE I.

Case Number	Years of Employment	Penicillium (Paczeskii) 100 pnu.	Penicillium (Paczeskii) 500 pnu.	Alternaria 100 pnu.	Aspergillus 100 pnu.	Household Dust (Conc.)	Ragweed 100 pnu.	Feathers (Mixed) 100 pnu.
1	5	—	—	—	—	+	—	—
2	11	—	—	—	—	+	—	—
3	15	—	—	—	—	+	—	—
4	22	—	—	—	±	+	—	—
5	23	—	—	—	±	+	—	—
6	26	—	—	—	±	+	—	—
7	28	—	±	±	—	++	++	+
8	30	—	—	—	—	+ (+)	—	+
9	30	—	—	—	—	+	—	±
10	30	—	—	—	—	±	—	±
11	30	—	—	—	—	+ (+)	—	±
12	30	—	—	—	—	+ (+)	—	—
13	30	—	—	—	—	+	—	+
14	32	—	—	—	—	—	—	±
15	33	—	±	—	—	+	—	—
16	38	—	—	—	—	+	—	—
17	38	—	—	—	—	± (+)	—	—
18	38	—	—	—	—	++	—	—
19	39	—	±	—	—	+	—	—
20	40	—	±	—	—	—	—	—

dishes to the air in different locations of an anthracite coal mine. Exposure was limited to fifteen minutes.

The number of colonies of fungi developing on each plate varied from five to fifteen. Transplants were made from the colonies of *Penicillium (Pac) Zaleskii* by inoculation into a medium consisting of crude dextrose four per cent, peptone one per cent, and tap water sufficient to make 100 per cent. The thick, fungous mat which grew on the surface of this liquid was collected, washed with 95 per cent alcohol and dried in a vacuum desiccator. Subsequent steps followed in the preparation of the extract were carried out in the allergy laboratory.

This investigation was begun in 1942. § Twenty individuals were studied for hypersensitivity to the mold at that time (Table I). The method of procedure was as follows:

Intradermal injections were made with the extract of the mold in dilutions containing 100 and 500 protein nitrogen units per cubic centimeter. The quantity injected into the usual area of the upper arm was approximately .02 c.c. Reactions were recorded upon the expiration of a period of ten minutes. They were rated as slight when the wheal formed measured not less than one-fourth of an inch in diameter. Doubtful reactions were ascribed to those which had shown wheals less than one-fourth of an inch, or circular erythema not less than one-half inch in diameter. Reactions which came below these requirements were considered as negative.

Seven (30 per cent) of this group of twenty workers gave slight or doubtful reactions. Six of these were workers who had engaged in mining for from thirty-three to forty years. One had engaged in mining twenty-eight years. Thirteen had employment ranging from three to five years.

In attempting to substantiate the findings in this first group under study,

§ W. Piekarski: Study of sensitivities due to molds in an occupational environment. Read before the Central Pennsylvania Allergy Society, September 25, 1946, Lancaster, Pa.
May JUNE, 1950

ROLE OF FUNGI—PIEKARSKI

TABLE II.

Cust. No.	Age	No. Years Employed	Penicillium (Pnacekii) Zaleski 100 p.n.u.	Penicillium (Pnacekii) Zaleski 1000 p.n.u.	Alternaria 100 p.n.u.	Aspergillus 100 p.n.u.	Household Dust (Cone.)	Mothy and Chard 0	Feathers (Mixed) 100	Brag Weed 100	Orris 100	Wool 100	Tobacco 1000
									++	++	++	++	++
1	10	10	++	++	++	++	++	++	++	++	++	++	++
2	12	12	++	++	++	++	++	++	++	++	++	++	++
3	13	13	++	++	++	++	++	++	++	++	++	++	++
4	18	18	++	++	++	++	++	++	++	++	++	++	++
5	18	18	++	++	++	++	++	++	++	++	++	++	++
6	20	20	++	++	++	++	++	++	++	++	++	++	++
7	20	20	++	++	++	++	++	++	++	++	++	++	++
8	20	20	++	++	++	++	++	++	++	++	++	++	++
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11	20	20	++	++	++	++	++	++	++	++	++	++	++
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31	20	20	++	++	++	++	++	++	++	++	++	++	++
32	20	20	++	++	++	++	++	++	++	++	++	++	++
33	20	20	++	++	++	++	++	++	++	++	++	++	++
34	20	20	++	++	++	++	++	++	++	++	++	++	++
35	20	20	++	++	++	++	++	++	++	++	++	++	++
36	20	20	++	++	++	++	++	++	++	++	++	++	++
37	20	20	++	++	++	++	++	++	++	++	++	++	++
38	20	20	++	++	++	++	++	++	++	++	++	++	++
39	20	20	++	++	++	++	++	++	++	++	++	++	++

ROLE OF FUNGI—PIEKARSKI

the following recent investigations were carried out in 1947-48. On this occasion, twenty-seven subjects were studied (Table II).

Tests were performed with strengths of 100 and also with 1,000 protein nitrogen units per cubic centimeter of the *Penicillium* extract.

Evaluation of the skin reactions was made with a reasonable degree of accuracy considering the usual inconvenience met with in dealing with bed-ridden patients. Ambulant cases comprised about 50 per cent of the workers studied.

In view of the low-grade reactions in the direct skin tests, passive transfer was not attempted. Results of the skin tests in this second series were as follows: When an extract of *Penicillium (Pac) Zaleskii* was used containing 100 protein nitrogen units per cubic centimeter, doubtful reactions were observed in five out of twenty-seven (21.3 per cent) cases studied.

One of these doubtful reactions occurred in an individual who had been employed fifteen years. Fourteen individuals had been employed thirty or more years. Four of these gave doubtful reactions.

When an extract was used containing 1,000 protein nitrogen units per cubic centimeter, two (7.4 per cent) out of a total number of twenty-seven cases gave 1-plus reactions and ten (37. per cent) others gave doubtful reactions. The remaining fifteen cases (44.4 per cent) were negative.

The majority of these reactions began to appear after the twentieth year of employment when the stronger extract was used, as compared with the minimal period of thirty years when the weaker extract was employed.

Two paradoxical cases were observed which gave doubtful reactions with the weaker extract (100 protein nitrogen units per c.c.), whereas the stronger one (1,000 protein nitrogen units per c.c.) gave negative results. Such discrepancies may be accounted for either by technical errors arising from faulty visibility in some sections of the medical ward, or by differences in the reception of the skin as found in some cases when intradermal injections are made into the proximal and distal parts of the upper arm.

About one-fourth of this group, consisting of seven out of twenty-seven employees, had shown reactions in the skin tests of 2-plus grade to household dust and of a lesser degree to other common inhalants. In general, these cases also had shown other evidence of clinical allergy or had given positive histories of allergy in their ancestors or/and descendants. In most cases, the maximum period of their engagement in the industry did not exceed thirty years. It may be assumed that in some of these cases, employment was curtailed in a greater or lesser degree by dyspnea of an allergic nature, in which the clinical manifestations either preceded or were superimposed upon varying degrees of pulmonary fibrosis resulting from inhalation of mineral dusts.

About 75 per cent of the workers have discontinued their occupation for periods ranging from one to ten years prior to the beginning of this study.

In the survey of this investigation, the question arises as to what extent allergy to the occupational mold may be responsible for the attacks of

ROLE OF FUNGI—PIEKARSKI

dyspnea? Whether the prolonged period of exposure to the concentrated atmospheric spores and other biologic structures of this organism had any influence on the skin tests in these cases is uncertain. Very likely, however, the skin manifestations were based on nonspecific reactions. According to vague results obtained in the latter procedure and failure to incite symptoms of bronchial asthma by insufflation of the environmental mold, the attacks of dyspnea are unlikely to be due to spontaneous or acquired sensitivities to the underground spores. On the basis of the foregoing studies it seems to be justifiable in assuming that the embarrassment of respiration in these cases is largely due to the following: (1) Fibrosis of the pulmonary tissues resulting from inhalation of mineral dusts which is accompanied by cor pulmonale in certain advanced cases.* (2) It may be due to upper respiratory infections commonly found in advanced cases of anthracosis.** (3) It is natural to assume that individuals showing moderate skin reactions to extrinsic factors, such as household dust, pollens, orris and feathers, may suffer clinical manifestations from this source. (4) Dyspnea due to other causes, such as foreign bodies in the respiratory tract, bronchogenic tumors, tuberculosis, et cetera, must be ruled out.

The essential findings of this study show the innocuous nature of concentrated atmospheric spores of *Penicillium (Pac) Zalcskii*, when inhaled by persons employed in the subterranean arteries for prolonged periods of time.

Another important feature brought out in this investigation relates to the use of penicillin as a therapeutic agent.

No unusual findings of an allergic nature, due to cross-reactions, were observed in these cases following its use as an antibiotic in the treatment of infections resulting from trauma or other causes. The use of this derivative of the genus, *Penicillium*, had met with the same degree of success in the treatment of those exposed to large numbers of occupational spores of this fungus as in persons of other walks of life.

In the limited number of cases presented in this report there were no histories referable to the ocular or nasal organs showing clinical manifestations of lacrimation and sneezing. Neither could these symptoms be elicited by insufflation of the occupational fungus under ordinary room temperatures. Whether or not a synergistic action of the fungus and the prevailing low temperatures of the underground locations plays a role in the production of these symptoms is open to further investigations.

SUMMARY

An investigation of the role of fungi in patients with bronchial asthma and anthracosis is reported.

The air of anthracite coal mines contains a large number of spores of

*Government bulletin: The Health of Workers in Dusty Trades. Exposure to Carbon Dust in Coal Mining. Survey of respiratory diseases in coal miners made during the period, January 1, 1924, to September 1, 1925.

**Physical examinations were performed on 344 coal miners. Findings recorded: bronchitis, 25; pleurisy, 3; pulmonary tuberculosis, 7; chronic rhinitis and pharyngitis in workers over forty-five years of age; pneumoconiosis, including anthracosis, 2%; asthma, 9.

ROLE OF FUNGI—PIEKARSKI

Penicillium (Paczeskii) Zaleskii and a smaller number of spores of *Stysanus Stemonitis (Pers) Corda*. These fungi thrive on nourishment derived from various kinds of timber and flourish with a luxurious growth of mycelium surrounding the ligneous structures.

A search for an acquired, or atopic, form of allergy due to occupational molds was made on forty-seven miners, most of whom were no longer employed for periods ranging from one to fifteen years, due to physical disabilities resulting from anthracosis with manifestation of bronchial asthma-like syndrome.

The study was made in two series. The first group was composed of twenty and the second consisted of twenty-seven unemployed persons with anthracosis. The first study was made in 1943, and the second in 1948.

The purpose of this investigation was primarily to learn if any atopic allergies existed to the inhaled spores of the occupational mold; also, whether or not, skin sensitization can be produced by inhalation, for long periods of time, of large numbers of spores of this fungus.

Observations were also made for symptoms expressed clinically in lacrimation and sneezing, said to be present in certain underground workers at times when they are exposed to an excessive growth of fungi.

Intradermal tests were made and the dried powdered mold was insufflated in the second series of workers studied.

In the first series of workers studied, the extracts used in the intradermal tests consisted of 100 and 500 protein nitrogen units. There seemed to be some correlation between the time of appearance of doubtful reactions in the skin tests and the period of exposure to the mold. All anthracotics whose time of employment in the coal mine exceeded thirty-two years showed such reactions. Six reactions were noted.

In the second series, the results were more disappointing. Only four out of fourteen patients whose former engagements in the industry exceeded twenty-eight years gave doubtful reactions in the skin tests, when an extract containing 100 protein nitrogen units per c.c. was used.

With the use of an extract containing 1,000 protein nitrogen units per c.c., eleven skin reactions were noted and they were nearly all doubtful. No uniformity existed as to the time of exposure and the appearance of doubtful skin reactions. Like the remainder of these tests, they were apparently based on nonspecific origin.

27 East South Street

IDIOBLAPTIC TOBACCO SENSITIVITY

GRANVILLE F. KNIGHT, M.D., F.A.C.A.
Santa Barbara, California

THE substances to which the human body may react in an abnormal or hypersensitive manner would seem to be legion.

The use of tobacco by a large proportion of our adult population in homes, offices and public places results in the widespread exposure of most people to tobacco smoke. It is not surprising, therefore, that a certain number of smokers and nonsmokers should report unpleasant reactions of varying severity from this contact.

In view of these reports it is of considerable importance to determine, if possible, the incidence of tobacco hypersensitivity, and to catalogue any harmful symptoms attributable thereto.

A quick review of the literature reveals a wide divergence of opinion as to the potentially harmful effects of smoking tobacco.

A number of observers^{3,6,7,9} have shown that in many individuals, smoking is accompanied by a temporary tachycardia, rise in blood pressure, elevation of the blood sugar, drop in peripheral temperature, changes in the electrocardiogram (arrhythmias and prolongation of the QRS interval) and decreased oxygen utilization by the superficial tissues.

Analogous changes have been produced by intravenous nicotine.^{6,7}

Harkavy⁵ demonstrated to his own satisfaction positive skin tests and the presence of tobacco reagins in 55 per cent of eight cases of thromboangiitis obliterans.

Hewell⁶ could not demonstrate positive skin tests in any cases studied by him. In a thorough study of twelve individuals he noted a tachycardia and rise of blood pressure in all. He explained this on the basis of idiosyncrasy to a common substance affecting certain individuals who have labile vascular systems. A few of his subjects did not react.

H. L. Segal⁸ reported six patients with chronic fatigue relieved by cessation of smoking. All had a pulse rise with smoking. He did not attribute this picture to any idiosyncrasy.

H. G. Hadley¹ in a study of pulse and blood pressure in 7,000 office patients, concluded that the tobacco habit increases the pulse rate but lowers the blood pressure. His observations are open to the criticism in that he included in the smokers group those who had smoked even one cigarette within three years!

Coca¹ has recently stressed the fact that while many smokers show a tachycardia and rise in blood pressure following the use of tobacco, a considerable number fail to show any observable change. He attributes this difference to the presence of nonreaginic allergy in the reactors.

The following observations were carried out, independently, after contact with Coca's work on nonreaginic food allergy in 1943. Until recently,

¹ Presented at the Fifth Annual Meeting of the American College of Allergists, April 14-17, 1946, Chicago, Illinois.

IDIOBLAPTIC TOBACCO SENSITIVITY—KNIGHT

acquaintance with the literature was purposely avoided so that preconceived ideas might not be acquired.

In attempting to work out problems of food allergy, according to pulse response, it was soon realized that tobacco itself was a major and, in some

DATE		NAME	
TIME	PULSE	DIET	SYMPOMS
BEFORE RIISING		BREAKFAST	
BEFORE BREAKFAST			
1/2 HR. LATER			
1 HR. "			
1 1/2 HRS. "		LUNCH	
BEFORE LUNCH			
1/2 HR. LATER			
1 HR. "			
1 1/2 HRS. "		DINNER	
BEFORE DINNER			
1/2 HR. LATER			
1 HR. "			
1 1/2 HRS. "		TOBACCO USED	
AFTER RETIRING			

DIRECTIONS
 131 COUNT PULSE FOR 1/2 MINUTE AND MULTIPLY BY 2.
 132 EXCEPT FOR THE MORNING AND EVENING, SIT DOWN FOR 3 MINUTES
 BEFORE TAKING PULSE.
 133 REFRAIN FROM ANY USE CONTACT WITH PAINT FUMES, SOAP POW-
 DER, SCENTED COSMETICS, OR ANY UNUSUAL ACTIVITY.
G F KNIGHT, M.D.

Fig. 1. (A) Pulse chart.

cases, the sole offender. Its ability to produce a persistent tachycardia throughout the waking hours of certain smokers, together with potentially serious symptoms, was deemed sufficient reason for this preliminary report.

METHODS

Observations were made on private patients who came to the office complaining of conditions which might be classed as allergic, as due to chronic infection, or a combination of the two.

Preliminary work included a careful history, physical examination, skin tests and laboratory work as indicated. Intradermal tests to tobacco were either negative or doubtful. No passive transfer studies were undertaken.

At the first visit, pulse and blood pressure readings were taken after the patient had been sitting down for five minutes.

All blood pressure readings were made from the right arm, with the same machine and by the same observer.

Any patient with a pulse rate over 72, a blood pressure higher than an arbitrary 126/76, or with a history suggesting idioblapsis, was asked to chart his pulse rate for a period of forty-eight hours and to list all food and drink taken. Readings were recorded before arising and after retiring, before each meal and three times afterwards at half-hour intervals. With the exception of the first two, which were recorded prone, the subject was asked to remain seated for three minutes before taking his pulse. Instruc-

IDIOPATHIC TOBACCO SENSITIVITY—KNIGHT

tions for taking the pulse were given and the patient's readings checked.

For the purposes of this paper only smokers were included.

At the second visit the significance of the pulse chart was explained and

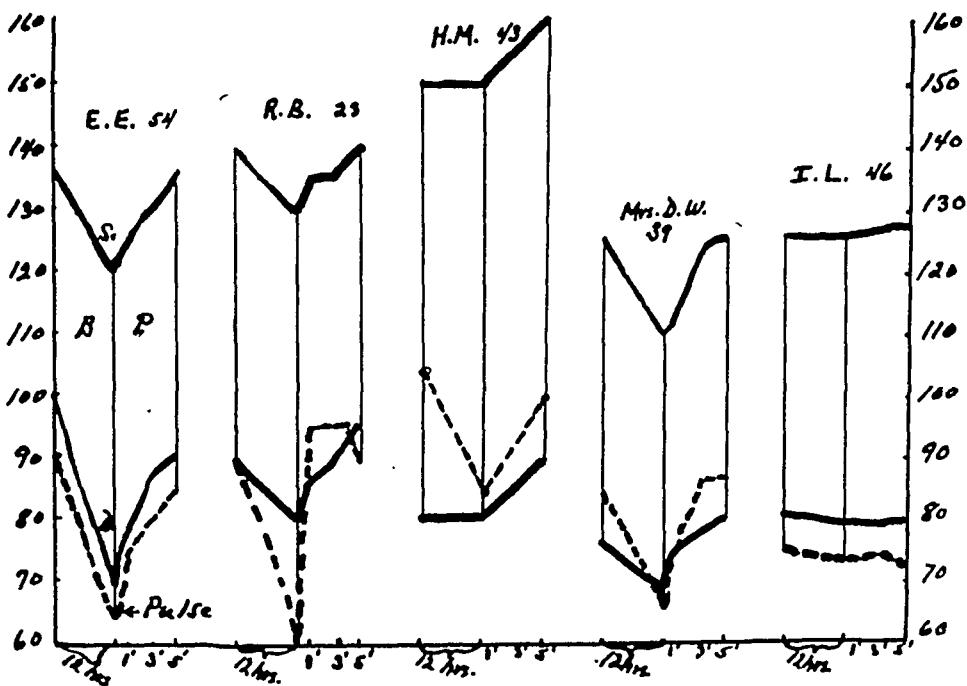


Fig. 1. (B) Various types of reaction to the smoking test.

pulse and blood pressure determinations again made. Tobacco consumption was estimated.

Those with charts showing a spread of 20 or more beats between the highest and lowest recorded pulse rates, or with a high which surpassed 90 were assumed to be allergic to tobacco, to foods or to other factors in the environment.

Patients willing to co-operate were then requested not to smoke after 10:00 p.m. and told to report the next morning between 10:00 and 12:00 a.m. This hour was chosen to rule out the possible effect on the pulse rate of foods taken at breakfast. Charting was continued.

SMOKING TEST

At this visit the patients had not used tobacco for twelve hours, and the great majority showed a significant drop in pulse rate and blood pressure. These readings were taken as usual after five minutes in the sitting position.

Patients were then asked to smoke a cigarette. Pulse and blood pressure were recorded at one, three, five and ten-minute intervals.

Early observations in sensitive individuals showed the tachycardia to begin within ten to thirty seconds and to reach its peak in three to five minutes. When a rise in blood pressure occurred, this roughly paralleled the pulse acceleration.

While Coca has postulated that subcapsular kidney edema may account

for idioblastic hypertension, the rapidity of the response to tobacco suggests that overactivity of the sympathetic nervous system and perhaps the adrenal medulla, with resultant vasospasm, may be of more importance.

If a definite rise of 10 points or more in pulse rate was noted while

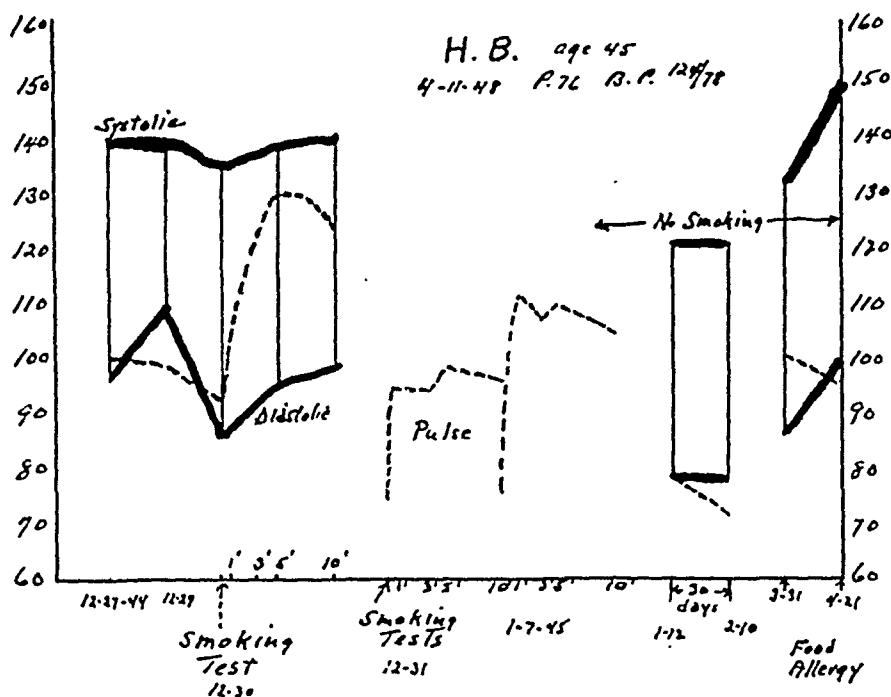


Fig. 2. Case 1. Marked tachycardia of at least ten years' duration, fatigue, nervousness and moderate hypertension relieved by cessation of smoking. Marked pulse reaction to tobacco. Recurrence due to food allergy relieved by elimination of offending foods.

smoking, patients were asked to stop tobacco, or to cut down cigarette consumption to a maximum of six taken between meals and during the evening and to continue with the pulse chart.

The effect of the new regime on the pulse was noted for forty-eight hours more and recorded by the patients. At the end of this time repeat observations were carried out in the office. Inquiries were made to bring out any changes which might have occurred in symptomatology.

GENERAL OBSERVATIONS

In many cases, restriction of tobacco resulted in a marked drop in pulse rate. Concomitant with this, there was noted in certain individuals a significant drop in blood pressure and/or relief from unpleasant symptoms. The following are worthy of mention: tachycardia, palpitation, extra-systoles, fatigue, depression, headache, vague fear sensations, insomnia, nervousness, tremor, post-nasal drip and stuffy nose, sleepiness in the afternoon, morning tiredness, tickle in pharynx and larynx, chronic cough, chronic bronchitis, gingival irritation, coated tongue, mild parotid swelling, hoarseness, neuralgic pains, cervical and interscapular myalgia or "tightness,"

IDIOBLAPTIC TOBACCO SENSITIVITY—KNIGHT

weakness of legs, joint pains and stiffness, constipation, decrease in olfactory and visual acuity. Other phenomena will undoubtedly be reported.

CASE HISTORIES

Case 1.—Mr. H. B., aged forty-three, was first seen December 27, 1944, complaining of post-nasal discharge and recurrent sore throat of two to three months' duration. History revealed the following: Subject to fall hay fever. Tonsillectomy and ade-

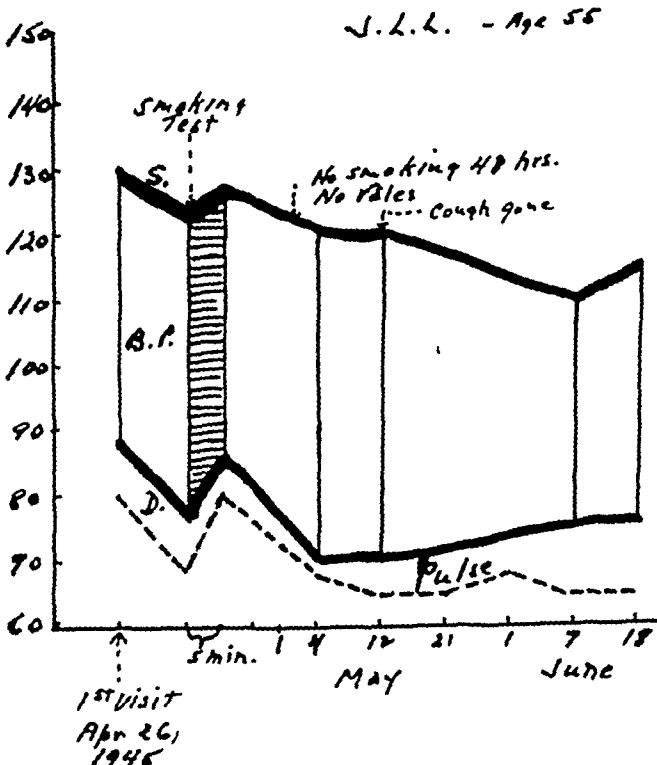


Fig. 3. Case 2. Severe morning and evening physical tiredness, much post-nasal drip, and more or less continuous wheezing and coughing for twenty years. Complete relief by avoidance of tobacco.

noidectomy as child. Remains treated with electric needle. Right antrum irrigated ten years ago. Rapid pulse since childhood; as high as 140 thirteen years ago, at which time vision in left eye decreased rapidly. Thyroid brought pulse down to around 100 and relieved the visual loss. Taking 5 grains of thyroid daily past ten years. Smokes about ten cigarettes in twenty-four hours.

Physical examination: Pulse 100, blood pressure 140/96. Antra dark. Tonsil fragments and linguals cryptic and inflamed.

Impression: Sinusitis, tonsillitis, hypertension, nonreaginic allergy.

Local condition improved with penicillin therapy to sinuses.

Pulse chart showed range of 68 to 136.

A smoking test after twelve hours' abstinence from tobacco showed a brisk reaction (Fig. 2).

He was advised to stop smoking and did so by the end of one week.

His pulse and blood pressure stabilized at normal levels as shown in the diagram, and he reported much less fatigue and increased muscular power as well as decreased nervous tension.

He came in again almost three months later, complaining of fatigue and the jitters and that his pulse was up again. He attributed this to lack of thyroid, his dose having been cut to 2 grains daily.

IDIOBLAPTIC TOBACCO SENSITIVITY—KNIGHT

A marked tachycardia and definite hypertension were again present. By means of a trial diet it was shown that sensitivity to a number of foods was now causing trouble. Elimination of these resulted in a relatively normal pulse and blood pressure which have persisted.

Last seen April 21, 1948. Pulse 76, blood pressure 124/78. Still gets occasional rise in pulse and blood pressure, especially in mornings, apparently from some inhalant allergen.

It is noteworthy that his hay fever was not relieved by this regime.

Case 2.—Mr. J. L. L., aged fifty-five, came to the office on April 26, 1945, complaining of much post-nasal discharge, more or less continuous wheezing and coughing and marked morning and evening fatigue over a period of twenty years. Worse past eight years. Weight loss, 10 pounds in past three years.

Past history revealed a family history of hay fever and asthma. Operation twenty years ago for carcinoma of epididymis. Much x-ray therapy. Checked seven years ago; apparently all right. Alcohol, about one drink monthly—more than one knocks him out. Used to smoke one pack of cigarettes—now about one-half pack.

Physical examination: Audible wheezing and bubbling râles. Stethoscope revealed coarse, moist râles both lungs. Pulse 78, blood pressure 126/80. Pulse chart lost.

A smoking test after avoidance of tobacco for twelve hours showed a comparatively slight, but as results proved, a significant reaction (Fig. 3). Avoidance of tobacco was advised.

Examination on May 1, 1945: No smoking, No audible râles. Cough better. Chest x-ray shows increased markings. His cough rapidly disappeared, his excessive fatigue vanished and he gained weight. He found that, much to his surprise, he could now take two or even three drinks on occasion without severe ill effects.

When last seen two years later at a social affair he reported that he was well and that the cough had not returned.

Case 3.—Mr. D. C., aged thirty-nine, a lawyer, was first seen in 1941 complaining of stuffy ears. Questioning revealed the presence of rather profuse, whitish nasal and post-nasal discharge, most marked upon arising. Mild psoriasis noted for five years. Diet satisfactory. Smoked one and one-half to two packs cigarettes daily. Alcohol used to mild excess over week ends. Worked under considerable pressure.

Physical examination: Pulse 70, blood pressure 115/80. Looks well. Nasal mucosa slightly pale and boggy. Examination otherwise negative except for coated tongue.

Skin tests to staple foods and a few common inhalants, including tobacco, were negative except for a slight reaction to tea and coffee.

Dietary management and removal of ear wax resulted in slight improvement in nasal symptoms and relief of ear complaints.

The patient returned two years later in June, 1943, for removal of wax. Post-nasal discharge worse, coughing in mornings sometimes inducing vomiting.

Physical examination: Pulse 80, blood pressure 150/100. Tongue shows marked yellowish coat. Wax removed. Laboratory work negative.

One week later: Pulse 96, blood pressure 146/96.

Pulse chart showed top rate of 96.

Advised to stop tobacco and alcohol and chart pulse.

Three days later pulse from 54 to 64, blood pressure 115/80. Cough and morning discharge 80 per cent gone. Tongue almost clean.

On June 26, six days later, the blood pressure was 130/80.

One June 29, nine days later, it was 110/60. Almost no cough or discharge.

A study of Figure 4 shows the effects of resuming alcohol a few days after starting the trial diet. While food allergens were suspected when his pulse rose into the

IDIOPATHIC TOBACCO SENSITIVITY—KNIGHT

70's, none could be demonstrated. It must be assumed that a carry-over from alcohol was responsible. The slight drop in pulse rate between (5) and (6) on the chart, when alcohol was stopped, is suggestive.

After a smoking test (8) this patient would no longer keep a chart, and the

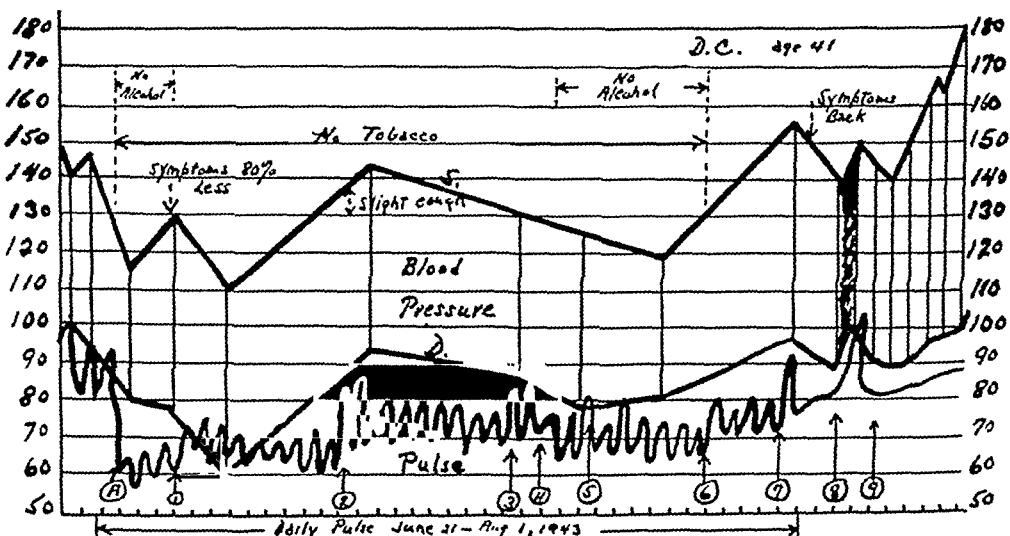


Fig. 4. Case 3. Disappearance of tachycardia, hypertension, excessive fatigue, cough and marked post-nasal drip following elimination of tobacco and alcohol, together with their reappearance upon renewed contact with these substances.

(A) Nothing except water after lunch. (1) 1 or 2 drinks daily. (2) 2 to 6 drinks daily. (3) After tennis. (4) Stopped alcohol. (5) Important business luncheon. (6) 2 or 3 drinks daily, plus 2 or 3 cigarettes. (7) Resumed smoking. (8) 5 to 15 cigarettes Old symptoms back. (9) No smoking five hours. Smoking test. Reading after 5 minutes on August 27, 1943. (9) Vertical lines indicate sporadic observations on September 17 and 30, 1943; December, 1944; October and November, 1945; August, 1946.

subsequent readings were made in the office when he appeared for treatment of colds or removal of wax.

At the last visit there was a marked tremor of hands, lips and tongue. The latter showed a heavy yellowish coat.

It is worthy of note that in spite of the evidence incriminating tobacco and alcohol, this patient refused to give them up. The psychological reason could not be uncovered, nor would a psychiatrist be consulted. The implications are challenging.

INCIDENCE OF TOBACCO SENSITIVITY

Time has not permitted a survey of all smokers tested. However, sixteen of the first 100 cases, or 16 per cent, failed to show any pulse response to the smoking test.

This figure differs considerably from Coca's report¹ of tobacco sensitivity in thirty cases solved by the pulse method. Here he found a specific tachycardia from tobacco smoke in only 50 per cent.

This marked discrepancy may be due to two factors:

1. The difference in the number of cases surveyed.
2. A summation effect, in the present series, of sensitivity to foods, alcohol, inhalants and tobacco.

For instance, it has been observed in several cases that ingestion of moderate and excessive amounts of alcohol the night before results in a higher

pulse rate the next day. The pulse response to tobacco in sensitive individuals is much more marked in the presence of this carry-over from alcohol.

Coca's cases, when tested to tobacco, were not under the influence of other allergens.

More work on this phase of the problem is indicated.

DISCUSSION

Unfortunately, many patients, sensing a frontal assault upon one of their ingrained habits, either retired disgruntled from the field or insisted upon treatment without further investigation of their tobacco sensitivity.

The majority were co-operative as far as the preliminary survey was concerned. But, unless suffering from very uncomfortable symptoms, or possessing unusual intelligence and fortitude, they refused to give up tobacco indefinitely.

Be this as it may, a number of sensitive individuals were impressed by the objective evidence shown by the pulse charts. These were helpful in upholding the analogy between an unnecessarily rapid pulse rate and the racing motor of a car with a slipping clutch.

It may be that in the future with increased knowledge of harmful effects from tobacco smoke, the physician can be firmer in his advice that sensitive patients should stop smoking. This would apply particularly to those with clinical signs or symptoms that have been found to be associated with idioblapsis.

SUMMARY AND CONCLUSIONS

1. While some individuals may smoke tobacco without any obvious cardiovascular response, others exhibit a specific tachycardia. This increase in pulse rate may be accompanied by unpleasant and potentially dangerous symptoms which, unless due to idioblastic allergy to other contactants or ingestants, or to irreversible changes, disappear with cessation of smoking. It seems logical to describe the reactors as allergic to tobacco smoke.

2. A simple and practical method of discovering this sensitive group is described.

3. Many smokers use tobacco frequently enough to maintain a tachycardia throughout their waking hours. While not all of these will complain of symptoms referable to the use of tobacco, it seems unlikely that overstimulation of the cardiovascular system over a period of years can be considered harmless to the human homeostatic mechanism.

4. Allergic individuals should be advised to stop smoking or to limit their consumption to the equivalent of six or eight cigarettes daily. Moderation seems to be impossible for most of this group.

5. Hypersensitive patients who do stop smoking should, for a period of six to eight weeks, fill out a twenty-four-hour pulse chart once weekly in

(Continued on Page 431)

MICROPOWDERED PROCAINE PENICILLIN BY INHALATION

GEORGE V. TAPLIN, M.D., WARREN GREENE, M.D., WALTER RALSTON, M.D.

WILLIAM ADOLPH, M.D., and LEONARD BAURMASH, B.Ch.E.

With the technical assistance of
MARY LOUISE GAUTSCHI, B.S., and HELEN BRUSCH, B.S.

Los Angeles, California

DURING the past year, there has been widespread clinical use of procaine penicillin by injection.^{2,3,4,12,13,14,22,29} The chemical combination of procaine and penicillin G, mole for mole, results in a true salt which retains the antibiotic activity of penicillin as well as some of the local anesthetic properties of procaine.

Procaine penicillin is a white substance with a characteristic crystalline structure. It is relatively insoluble, non-toxic, and non-irritating to body tissues or mucous membranes. If this compound is micropulverized and suspended in oil or aqueous solution, the resulting suspension is absorbed at a slow rate after intramuscular injection. Blood concentrations in a therapeutic range have been consistently attained for twenty-four hours or longer. If the same substance is mixed with a water repellent, such as 2 per cent aluminum monostearate, the individual particles are coated and the rate of absorption is decreased. Thereby the interval between injections may be greatly prolonged. Procaine penicillin is considered to be the most satisfactory repository type preparation now available commercially. This is particularly true when the crystals have been reduced to a fine powder (5 microns or less) prior to suspension in a vehicle containing aluminum monostearate.

Because of the properties of procaine penicillin mentioned, it was decided to investigate the use of microcrystalline procaine penicillin by inhalation. Preliminary studies revealed that such powders were almost odorless, tasteless, and non-irritating to the nasal and pharyngeal mucous membranes. Prior to extensive clinical trial, bacteriologic assays were made to measure the absorption rates of procaine penicillin from the respiratory tract following oral and intranasal inhalations. It was soon observed that the rates of absorption are two to four times slower compared with those following sodium penicillin preparations having approximately the same particle size distribution. For example, 100,000 units of procaine penicillin gives detectable blood levels for six to eight hours compared with two to three hours following the intranasal inhalation of sodium penicillin.

The major purpose of these preliminary investigations with procaine penicillin micropowders was to determine the incidence of allergic reactions, both local and systemic. Inasmuch as procaine itself is an allergen,²⁹ it was necessary to demonstrate clinically whether inhaling the chem-

From the Investigative Medicine Service, Birmingham Veterans Administration Hospital, Van Nuys, California, and the Department of Medicine, School of Medicine, University of California at Los Angeles.

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PENICILLIN BY INHALATION—TAPLIN ET AL

ical combination of procaine and penicillin caused more allergic reactions than the inhalation of pure crystalline sodium or potassium penicillin salts. Although the incidence of allergic reactions after intramuscular injections of procaine penicillin is not reported to be higher than that following intramuscular administration of sodium penicillin in saline solution,^{6,8,15,19,23} it was essential to demonstrate whether the same relation existed following inhalation therapy.

TABLE I. PARTICLE SIZE DISTRIBUTION OF THE MICRO-POWDERED PROCAINE PENICILLIN PREPARATION USED*

Size Range (Microns)	No.	Number Per Cent	Surface Per Cent	Weight Per Cent
Below 1	46	15.3	0.24	0.02
1-2	92	30.7	1.40	0.16
2-3	31	10.3	1.45	0.28
3-4	14	4.7	1.30	0.36
4-5	18	6.0	2.85	1.01
5-10	61	20.3	29.42	18.80
10-15	27	9.0	31.80	31.07
15-20	8	2.7	19.94	28.09
20-25	3	1.0	11.58	20.21

Note: 300 particles were counted with the light optical microscope at 970 magnification using immersion oil on both surfaces of the microscope slides.

*Generously supplied by the Lederle Laboratories, Division of American Cyanamid Company.

PARTICLE SIZE DISTRIBUTION

Light and electron microscope examinations were made to determine the crystalline structure and the particle size distribution of this preparation. The mean particle size computed by numbers was found to be 1 to 2 microns, whereas it was much larger when computed by surface area and weight (Table I). The crystalline structure is shown in Figure 1.

RESPIRATORY TRACT RETENTION

After the intranasal inhalation of procaine penicillin powders, the expired air may be measured for penicillin content by immediately exhaling into a measured volume of buffered saline through a glass tube containing an absorbent cotton filter. Also, by gargling with measured amounts of saline immediately after each inhalation, the amount of penicillin deposited in the mouth and pharynx may be estimated by assaying these washings for penicillin.²⁴ The results of these experiments demonstrate that more than 99 per cent of the inhaled dose is retained in the respiratory tract. The greatest portion is deposited in the nasal passages.

The particle size distribution of the crystals present in the exhaled air may be demonstrated microscopically by exhaling directly on to a microscope slide and covering the mist-laden area with a coverslip. Most of the exhaled procaine penicillin may be seen to consist of extremely fine particles measuring 1.0 micron or less, and a few particles approximately 2 to 3 microns, greatest dimension. This observation is in accord with the work of Hatch, et al, who have shown that for complete pulmonary penetration

and maximum alveolar retention dusts must include a particle size range varying between 0.2 and 2 to 3 microns.¹¹

CLINICAL MATERIAL AND DOSAGE SCHEDULES

The majority of patients studied were adults of both sexes, twenty to sixty years of age. The following types of infections were treated: acute



Fig. 1. Photomicrograph of procaine penicillin micropowder demonstrating characteristic crystalline structure. Magnification 600 times.

nasopharyngitis, acute and chronic bronchitis, acute tonsillitis, acute sinusitis, acute and subacute cervical adenitis, acute laryngitis, and chronic bronchopulmonary disorders—primarily bronchiectasis with and without asthmatic manifestations.

The percentage of allergic individuals included was greater than that occurring in the general population. Also several cases of asthmatic bronchitis and bronchiectasis with associated allergic asthma were purposely treated. All patients were questioned as to the presence of common allergic manifestations, the occurrence of previous penicillin sensitization, and any history of untoward reactions immediately following the injection of procaine solutions. A record of any penicillin therapy administered during the past two years was also kept.

In the treatment of acute respiratory infections, the average dosage schedule used was 100,000 units inhaled two or three times daily for two to five days. The same dosage was given for seven to fourteen days for

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TABLE II. ANALYSIS OF ALLERGIC REACTION AND CLINICAL RESPONSE TO INHALED PROCAINE PENICILLIN MICROPOWDERS

Case Groups by Diagnosis	No. of Cases	No. Cases Prev. Treated with Penicillin	No. of Known Allergic Cases	No. Cases Prev. Sensitized to Penicillin	Allergic Reactions		Clinical Response		
					Local	General	Excellent	Good	Poor
No disease Volunteers	20	8	2	0	0	0	—	—	—
Acute Nasopharyngitis	48	28	6	2	0	2	22	16	10
Acute Tracheobronchitis	33	25	13	4	(1) 2	(1)	15	16	2
Acute Sinusitis	10	8	3	0	0	0	8	1	1
Chronic Sinusitis	5	4	0	0	(1) 1	(1)	0	2	3
Acute Tonsillitis	5	1	0	0	0	0	4	1	0
Bacterial Pneumonia	4	2	0	0	0	0	3	1	0
Chronic Bronchitis and Bronchiectasis	6	4	0	0	0	0	3	2	1
Broncho Pulmonary Infection with Asthma	9	8	7	2	0	0	4	3	2
Misc. Respiratory Infection, e.g., Laryngitis and Cervical Adenitis	10	5	1	1	0	0	5	5	0
Totals	150	93	32	9	5	4	64	47	19

Note: Parenthesized numbers indicate that one person exhibited a local and a general reaction. Nine reactions occurred in seven individuals.

chronic infections and some acute infections which required more prolonged treatment. One individual received 300,000 units daily for one month by intranasal inhalation. Several patients with bronchiectasis have been given seven to fourteen day courses of procaine penicillin by inhalation during the past year. An attempt was made to treat common upper respiratory tract infections only when the manifestations were most frequently caused by the action of bacteria rather than during the early stages when symptoms were presumably of virus origin.

CLINICAL RESULTS AND INTERPRETATIONS

In general, this regime of procaine penicillin inhalation therapy has been found to be satisfactory clinically. Almost all of the patients voluntarily declared a preference for the procaine salt to similar micropowders of sodium penicillin. Several persons who discontinued therapy before completing the prescribed schedule obtained satisfactory clinical results. A rather surprising observation noted by 110 of the 150 cases was symptomatic relief of sore throat, nasal discomfort, and associated headache, almost immediately or within a few hours. Three pneumococcal pneumonia cases were treated successfully with this form of penicillin therapy. A fourth individual received an initial injection of 300,000 units of procaine penicillin in oil followed by a seven-day course of inhalation therapy at home and responded satisfactorily. Two patients with a diagnosis of chronic bronchitis failed to respond to intramuscular injections of penicillin in oil in adequate dosage but obtained lasting relief after inhalation therapy. An analysis of the clinical results and allergic reactions from inhaled procaine penicillin is shown in Table II.

The interpretation of the patient's responses to inhaled procaine penicillin, was based on clinical observations and evaluation in each case. The

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criteria used included the following: the type and severity of the infection, the duration of symptoms prior to treatment, past history referable to similar episodes, their severity, usual duration and complications; plus the completeness and rapidity of recovery or sustained relief of signs and symptoms of the infection.

Response to therapy was classified as excellent, if all symptoms and signs were definitely improved within twelve to twenty-four hours followed by rapid recovery and no recurrences or complications. The clinical result was considered good if the same responses were obtained within twenty-four to seventy-two hours. The response was classified as poor if there were little or no shortening of the usual duration of the infection, incomplete relief of signs or symptoms, or if recurrences or complications appeared during or soon after completing a course of treatment.

Based on this classification, the intranasal inhalation of micropowdered procaine penicillin is considered an effective form of treatment for acute bacterial infections of the upper respiratory tract (130 to 150 cases). If the cases of acute nasopharyngitis and chronic sinusitis are excluded, the response is almost uniformly good (ninety of ninety-six cases). The ten failures among the forty-eight patients classified as having acute nasopharyngitis demonstrate that the manifestations frequently may be caused by organisms insusceptible to the action of penicillin. However, the observation that fifteen of these forty-eight patients obtained rapid relief and uncomplicated recoveries provides indirect evidence that penicillin sensitive bacteria are involved in the pathogenesis of these diseases.

CLINICAL ADVANTAGES OF PROCAINE PENICILLIN

Procaine penicillin micropowders are an improvement over similar sodium or potassium penicillin preparations since they are:

1. Less irritating to nasal and pharyngeal mucous membranes.
2. Less disagreeable in taste and odor, more pleasant to inhale, and tolerated by young children.
3. Less hygroscopic, and remain dry and dispersed, they require less time and effort to inhale.
4. Mildly anesthetic, they frequently give prompt symptomatic relief from nasal inflammatory processes.
5. Relatively insoluble, they remain in contact with mucous membranes longer, and provide continuous local antibiotic action.

REACTIONS TO INHALED PROCAINE PENICILLIN

The incidence of all allergic reactions has been seven cases in 150. Three known atopic individuals developed mild generalized urticarial reactions between the third and fifth days of treatment. There were no associated local reactions in the nose or throat. The fourth case had a pre-existing epidermophytosis of the hands and feet and developed an exacerbation of these lesions on the seventh day of treatment. This patient, a non-allergic

individual, had neither received penicillin nor experienced any reaction to procaine injections previously. He developed an allergic inflammation of the nasopharyngeal mucous membranes also, characterized by swelling and itching of the nasal passages and moderate infraorbital facial edema. The local and systemic manifestations persisted for approximately five days and were moderately well controlled by the oral administration of Neo-antergan (200 mg. per day in divided doses). The fifth case, an atopic individual, developed an allergic nasal reaction similar to that seen in the fourth case. He also suffered an activation of his epidermophytosis but it was less severe and of shorter duration. Two other allergic persons developed local reactions. One sustained slight nasal congestion and the second a mild perioral edema which followed administration by oral inhalation. Both of these disturbances were considered to be penicillin sensitization reactions. These individuals had suffered other allergic disturbances previously from other allergens. Six of the seven persons exhibiting allergic reactions were known to be hypersensitive individuals.

DISCUSSION

The 4.6 per cent incidence of allergic reactions observed in this group is almost identical with that encountered following the inhalation of sodium or potassium penicillin micropowders. The procaine salt of penicillin appears to be no more allergenic than sodium penicillin in the purified crystalline state. This series, however, includes a larger proportion of individuals with allergic histories or definite manifestations of allergy (thirty-two in 150) than is encountered in the general population. Ninety-three of these people are known to have received penicillin by inhalation or intramuscular injection in the recent past. A few of these individuals may have been sensitized to penicillin unknowingly. Therefore, the 4.6 per cent reaction incidence observed in these 150 patients indicates that procaine penicillin is probably less allergenic and may produce fewer reactions than reported (4.9 per cent) in our larger sodium and potassium penicillin series^{5,20,27,28} and by Krasno et al (3 to 6 per cent), who used sodium penicillin dust.^{16,17,18}

Procaine therapy by intravenous injection has been shown to alleviate allergic reactions caused by foreign serum and other allergens and has been reported to be a useful drug for various manifestations by hypersensitivity.^{1,7,21} Therefore, this action may be responsible in part for the apparent reduction in antigenicity of penicillin when it is combined chemically with procaine. It is also possible that a decreased rate of absorption favors the development of fewer sensitizations.⁹ Another plausible explanation for the relatively lower incidence of local allergic reactions (five in 150) is that comparatively few persons have been locally sensitized to the procaine penicillin salt. In addition, it has been reported by Haley et al¹⁰ that one of the important mechanisms of local action of various antihistaminic agents is vasoconstriction. Capillary constriction may be a sig-

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nificant factor in the pathogenesis of mucosal sensitization. It could assist in decreasing the rate and amount of procaine penicillin absorption from the respiratory membranes.

The authors are not aware of studies pertaining to the fate of procaine penicillin in body tissues. The unaltered incidence of systemic allergic reactions noted during this investigation (four in 150) indicates that penicillin probably dissociates from the procaine salt in body tissues and then acts in its usual manner regarding its sensitizing properties.

SUMMARY

The intranasal inhalation of micropulverized procaine penicillin G in 100,000 unit doses two or three times daily, has been found to be an improvement over sodium or potassium penicillin micropowders when administered for similar purposes.

There has been no increase in the incidence of allergic reactions over that observed following the inhalation of sodium or potassium penicillin dusts. The chemical combination of procaine with penicillin reduces the local anesthetic activity of procaine and possibly alters the local antigenicity of penicillin while it remains chemically combined. No reactions attributable solely to procaine have occurred. Atopic individuals and patients sensitized by previous penicillin or procaine administration should not be treated with procaine penicillin salts indiscriminately because they are prone to develop allergic manifestations.

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Plan now to attend the Seventh Annual Congress of The American College of Allergists February 11-14, 1951, to be held at the Edgewater Beach Hotel, Chicago.

EXTREME SENSITIVITY TEST REACTIONS TO SILK IN A NEGATIVE SKIN-TEST POLLEN PATIENT

A Clinical Study

I. S. KAHN, M.D., F.A.C.A., and J. W. H. ROUSE, M.D., F.A.C.A.
San Antonio, Texas

MISS C. L. R., aged twenty-eight, a secretary, was referred by Dr. C. J. Boehs, an otolaryngologist, and first seen on June 20, 1944. She has been under observation in our office ever since, in all some five years. The reference diagnosis was vasomotor rhinitis of considerable severity, without other nasal abnormalities, of three years' duration. According to the patient, the symptoms seemed a little less severe during the summer months of the first year of her trouble, but for the past two years the nose had never been clear except for a few hours at a time when under medication for the purpose. It was later shown that such local nose medication had no bearing on the case. The symptoms were worse at night, perennial in character and without seasonal variations. There were no known clinical food sensitivities; and, while under our care, foods were shown not to be important.

DIAGNOSTIC SKIN TESTS

Dermal: Pollen, foods, cottonseed, flaxseed: all negative. Wool, horse and cat hair: slight + positive. Silk: ++++.

Intradermal: Pollens—1:500 dilutions: negative. Fungi—1:400 dilutions; negative. House dust—1:5000: ++. Foods—Negative except +++ to tomato, of no clinical significance. Silk (later, January 5, 1945) 1:50,000: +++++. January 29, 1945 1:5,000,000: +++.

The silk extracts used were dilutions of a standard Lederle silk extract for intradermal testing. The undiluted material was used for scratch tests.

This same extract has been included for many years in our routine dermal testing set, and in its use in over a thousand cases we have seen only one or two strong positive reactions. This case showed no dermal lesions—the usual clinical response to silk allergy, and there was no discoverable silk contact. There was no known contact with animal dander.

In view of the perennial symptomatology and the nocturnal increase of symptoms, this case was rather naturally classified as one of silk, house dust, and bedding etiology; the usual precautions of avoidance of such contacts were instituted, including impervious, dust proof pillow and mattress covers. The patient's story of improvement in summer the first year of trouble added to the probability of this diagnosis. Subsequent events lead to doubts of the correctness of her observations on this point.

TREATMENT

1. The silk dermal test was done weekly as a therapeutic measure eight times, always with the usual +++ reaction. Later this was changed to 0.01 or 0.02 c.c. of a 1:5,000,000 dilution of this standard silk test extract. Eleven of such treatments were given, always with a +++ or ++++ local reaction.

2. Coseasonal intradermal treatment of our current spring and summer pollens, timothy for our grasses, carelessweed, and mesquite, using 0.01 or 0.02 c.c. of the 1:500 dilution and, later, the usual preseasional subcutaneous treatment with a mixture of equal parts of these pollens.

3. Preseasional subcutaneous ragweed, and, later, coseasonal intradermal treatments, using 0.01 or 0.02 c.c. of the 1:500 dilution.

4. The same for our midwinter cedar season.

5. Ascending doses of house dust.

REACTIONS TO SILK-KAHN AND ROUSE

There was absolutely no diagnostic justification for the use of pollen in this case. It was included in the treatment merely as a possible accessory secondary factor, as negative skin-tests pollen cases often complicate cases in our community definitely sensitive clinically to other positive skin test factors.

In view of the fact that ascending doses of pollen given with the house dust produced only minimal local reactions, and no obvious systemic disturbances, such minimal local reactions were disregarded, and dosage increases continued in the same manner. During this period we regarded this case still merely as one of house dust etiology difficult to desensitize.

The first evidence of pollen being a factor in this case occurred on February 1, 1945, when 0.16 c.c. of the 1:10 dilution of the timothy, carelessweed and mesquite mixture used as preseasonal subcutaneous treatment gave a ++++ delayed local induration. Ten days later, one-half this dose gave an immediate +++) local reaction. Doses were at once reduced to the non-reacting 1:50 dilution. There was little or no improvement during all this time.

In May 1946, after a year of handling, or, more correctly speaking, of mishandling, our eyes were finally opened to the air-borne pollen factors in this case with definite clinical proof. During that month, the patient took advantage of a two and one-half weeks' vacation, to embark on a bus tour to the City of Mexico. Here in San Antonio, at her departure, the nasal symptoms were of the usual severity, but they cleared at once on reaching the City of Mexico three days later, and they continued clear during the entire stay there. This symptom-clearing was of decided significance for two reasons:

1. Mexico City is practically free of antigenic air-borne pollen at that time of year.
2. Her house dust contact in Mexico City was far greater than in her local San Antonio environment.

The clearing of symptoms under these conditions practically eliminated these house dust and silk factors as being of clinical importance. Further definite confirmation of the pollen influence in this case was seen from subsequent events. The last 300 miles of the 800-mile return bus trip, especially the last 150 miles, brought the patient into contact with roadside and field pollen. She had no more than reached the beginning of this last 150 mile point at the Texas-Mexico border when nasal blockage and severe catarrhal symptoms immediately recurred, persisting for months. We had therefore definite confirmation of pollen or pollen and fungus etiology and could rule out silk and house dust.

From this point on, this case was considered correctly, as one requiring appropriate pollen treatment and correct pollen dosage. After going over our initial pollen doses, it was decided that our patient was actually more sensitive than we had thought, and needed more attention paid to minimal local reactions and post-treatment symptom exacerbations.

With our midwinter cedar, spring trees, grasses, carelessweeds, mesquite and fall ragweeds, we have some five successive pollen seasons in San Antonio and in some years we have antigenic atmospheric pollen continuously present from early or mid-December to the middle or end of November. Positive skin test cases are seen embracing several and, at times, all of these seasons. In addition, negative skin test pollen cases, especially of the low degree of sensitivity type, are not particularly rare in our community, both the uniseasonal and multiseasonal types, and occur with or without positive skin tests to other antigens both relevant and irrelevant. Local conditions probably account for the appreciable percentage of negative skin test pollen cases seen in our community. In the absence of any single perennial pollination factor, such perennial symptomatology in our opinion necessitated the inclusion of all the important pollens of at least four of our important pollen seasons extending from mid-December to the middle or end of November, because we often

REACTIONS TO SILK—KAHN AND ROUSE

have years in San Antonio with only three or four weeks of freedom from atmospheric antigenic pollen. This state of affairs requires multiple injections and concurrent preseasonal, coseasonal and perennial treatments at each visit in a patient having symptoms, and presenting at most visits a problem of differential diagnosis between underdosage, overdosage and the possible omission of some current airborne pollen. Obviously the handling of all cases of this type is difficult. As a matter of fact, it required one and one-half to two years of weekly visits in this particular instance to secure any improvement. In November, 1946, fungi were added, again empirically, in spite of negative skin tests.

Following her return from Mexico this case was treated perennially with five separate injections.

1. Ragweed.
2. A mixture of equal parts of oak, hackberry and pecan.
3. A mixture of equal parts of timothy, carelessweed and mesquite.
4. A mixture of equal parts of Alternaria and Hormodendrum.
5. Cedar.

In addition, booster coseasonal intradermal pollen treatments were given as needed; only pecan, with a pollination season of only a few weeks in the spring, gave any appreciable local reaction. For the last eight months, there has been no vasomotor rhinitis and almost none for four months previous. A ++++ scratch test to silk is still present. Also, the patient continues to work in the same office and lives in the same environment. If she had been sent to the Texas seacoast when first seen, the pollen etiology would, in all probability, have been established immediately. Direct intranasal or ocular pollen applications might also have been given in earlier confirmation. After the clinical demonstration, there was no particular advantage in applying these testing methods.

The patient toured Europe from mid-July to mid-September, 1949, with no nasal symptoms, although no precautions were taken against silk or house dust.

No attempt is being made to account for the extreme variation between the highly positive skin tests to silk and the negative pollen-fungi tests that were actually the basis of the symptoms. However, with an individual employed in or contemplating employment in a silk mill, this silk reaction would undoubtedly have been a decided clinical significance which was completely lacking in this instance.

SUMMARY

The case history is reported for a patient exquisitely sensitive dermally and intradermally to silk and with negative intradermal tests to pollen and fungi. She was shown clinically to be a pollen and possible fungus case, and not at all sensitive to silk.

1708 Nix Professional Building

Keep up with the newest developments in the treatment of allergy by attending the Graduate Instructional Course sponsored by The American College of Allergists at the Edgewater Beach Hotel in Chicago, February 9-11, 1951.

IMPOTENCE—AN UNUSUAL SIDE REACTION IN ANTIHISTAMINIC THERAPY

SIDNEY W. JENNES, M.D., F.A.C.A.
Waterbury, Connecticut

NUMEROUS reports have appeared in the literature concerning the occurrence of side reactions in the use of the antihistamines. Drowsiness, dizziness, nervousness, palpitation, headaches, nausea, diarrhea, weakness and dryness of the mouth were the allergic manifestations most commonly noted. Others reported of less frequent occurrence have been abdominal pain, bleeding from the rectum and premature menses.

A rather unusual side effect has been found by the author in two cases—that of impotence. In the first case, Pyribenzamine was the drug used; in the second, Pyribenzamine and Thephorin.

Case 1.—This patient was a twenty-six-year-old white laborer, who came to my office in June, 1947, with a history of urticaria of ten days' duration. Pyribenzamine, 50 milligrams three times daily, had been prescribed by his family physician, and it gave him some temporary relief from the itching. However, he complained that on the fourth day of Pyribenzamine therapy, he developed sexual impotence. This he considered worse than the urticaria itself, since he had been married only three months. On discontinuance of the Pyribenzamine, he was able to have normal erections; the urticaria became worse. However on elimination of several offending foods, the urticaria cleared up.

Case 2.—The second patient was a forty-three-year-old white male clerical worker who was first seen by the author on June 9, 1948. He gave a history of itching with welt formation, which began a year previously and had become worse during the past six weeks. Bathing aggravated his symptoms. The patient had a long past history of terminal ileitis of seventeen years' duration, during which period he had had four major operations, the last in 1946. His referring physician had given him Pyribenzamine, 50 milligrams four times daily, in May, 1948, which, as he put it, "knocked me out." In addition, it caused sexual impotence. After he stopped this medication, the impotence cleared up. His medication was changed to Benadryl, which in 50 milligram dosage caused drowsiness but not any sexual changes. During the course of study, I prescribed Thephorin, 50 milligrams three times daily, which after administration for four days produced impotence. Virility returned again after Thephorin had been discontinued for two days. The impotence had not returned in two months. He is taking no antihistaminics.

COMMENT

Two cases are reported of sexual impotence in male following administration of antihistaminics. In the both cases, Pyribenzamine, an ethylenediamine derivative, caused this unusual side reaction. In addition, in the second case, Thephorin, which is chemically unrelated to Pyribenzamine and has no related sedative action, also produced sexual impotence. Benadryl, a drug closely related to Pyribenzamine, did not cause this in the second patient.

In both cases, the impotence cleared up with immediate discontinuance of the drugs, though the allergic condition either became worse or continued unabated. No relation existed between the loss of virility and the primary allergic condition.

135 West Main Street

MAY-JUNE, 1950

Progress in Allergy

ANTIHISTAMINIC AGENTS

A Review

ETHAN ALLAN BROWN, M.D., F.A.C.A.

WILFRED KRABEK, M.S.

Boston, Massachusetts

(Continued from the March-April issue.)

The varying reports of the response of patients with bronchial asthma to anti-histamine drugs lead to a number of studies. In four asthmatic patients treated by Walton and Kristjanssen-MacDonnell,¹⁶⁹ the drug intensified symptoms. In the series by Guchs et al¹⁷⁰ all of the thirty patients presented a long history of bronchial asthma resistant to the usual measures. In twenty-eight there was demonstrable organic disease of the sinuses, lungs or heart. In eleven there were no skin tests and in nineteen there were skin sensitivities and chronic infection. The patients were observed for six months, while taking up to 500 mg. daily. Seven patients reported symptomatic relief, of whom two obtained similar relief with a placebo. All of these were free from organic, heart or lung disease. Twenty-three patients reported no relief. In all of these, secondary pathological lesions were present, but Benadryl appeared, however, to enhance the effect of the antispasmodic drugs added when the Benadryl alone was found to be ineffective. The drug had no effect on severe asthmatic attacks. In only three patients were the side effects sufficiently severe to warrant discontinuing treatment, although 93 per cent of the patients presented some side reactions. In the series by Rubitsky et al¹⁷¹ there were fifteen acutely ill asthmatic patients, eight of whom were intractable. Benadryl or Pyribenzamine was administered by rectal, aerosol and intravenous routes, the doses ranging from 20 to 50 mg. intravenously given at a rate of not more than 10 mg./minute. Once the severe bronchospasm was relieved, the patients were maintained with Pyribenzamine, 2.5 per cent, solution by aerosol alone, or mixed in equal parts with a bronchodilating drug. Ten of the fifteen patients obtained significant relief, or restoration of epinephrine sensitivity. The side reactions, however, included drowsiness, dizziness, headache, transient chilliness, nausea and fatigue. In one patient the vital capacity increased from 1300 to 2300 c.c. Six inhalations of Isuprel aerosol increased the vital capacity an additional 500 c.c. The best results were obtained in those patients who had previously been found to be histamine-sensitive. The duration of relief with the aerosol method was three to four hours and with the intravenous route, six hours. The oral medication brought on relief in sixty to ninety minutes and the rectal medication in fifteen to thirty minutes. Confirmatory results were reported by Friedman¹⁷² who treated twelve patients with Benadryl aerosol solution, to which penicillin or other antibiotics were added when indicated by the presence of infection. Nine of the patients had previously been treated with various systemic anti-histamine preparations, only two receiving benefit. Prophylactic administration of Benadryl aerosol prevented acute attacks or increased the intervals between attacks, decreasing their severity. None of the patients developed resistance to the drug, but two patients required increased doses after prolonged administration. In only two patients were there side reactions as marked by headache. One additional patient suffered from dry mouth.

Spirometric studies in sixteen patients with extrinsic bronchial asthma given

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Benadryl, 100 mg. orally shortly after the onset of a moderately acute attack of asthma showed no changes in vital capacity, tidal air, minute ventilation, expiratory differential, respiratory rate or degree of emphysema as noted by Levy and Seabury.¹⁷³ Six patients stated that there was complete relief of their dyspnea; five of the sixteen patients subsequently given ephedrine and aminophylline showed an increase in vital capacity, tidal air, minute ventilation and respiratory differential. There was, however, no increase in respiratory rate. No marked effect was seen in one patient with emphysema. The side reactions are described as vertigo, dry mouth, drowsiness, anxiety, weakness, epigastric pain, nausea, difficulty in co-ordination, feeling of mild inebriation, blurred vision, tinnitus, extreme dyspnea, palpitations, and it should be noted, precipitation of status asthmaticus. The drugs may act intravenously when not effective orally as shown in the report of Goldman.¹⁷⁴ All of his fourteen patients had not responded to Benadryl. In nine cases of urticaria there was immediate improvement, disappearance of swelling and alleviation of symptoms. One case of contact dermatitis was relieved from itching, partially, and in a second case, quickly. There was little effect in three cases of asthma. The dose most commonly employed was 10 mg. four hourly, the schedule being employed in one instance as long as twenty days, no patients demonstrating toxic effects.

Of 100 patients given Benadryl orally by Barksdale and Hall,¹⁷⁵ twenty-two of twenty-five patients with poison ivy and ten of twelve with chronic urticaria, as well as fourteen with acute urticaria of unknown origin, two of fifteen with atopic dermatitis, and three patients with hay fever were relieved. Benadryl was useful in the urticaria due to penicillin and effective as well in that due to streptomycin, trichophytin, merthiolate and sea food sensitivity. Patients, however, with dermatographia, erythema multiforme, scabies, psoriasis or idiopathic pruritus were not relieved. In six patients it was necessary to discontinue the use of the drug because of the unpleasant side reactions, which included those usually described and, in addition, "contractures of the arms and legs." In two patients with hay fever there were withdrawal symptoms as demonstrated by nausea.

As soon as new antihistaminic agents began to make their appearance, comparisons between them were in order. In this regard, one of the best papers is that by Loveless and Brown¹⁷⁶ who used Benadryl in fifty-three patients and Pyribenzamine in 150, the dose being 50 mg. orally repeated in one to four hours if necessary, but not more often than five times in any twenty-four hours. Constitutional reactions following overdosage with therapeutic allergens responded best, and then in decreasing order, acute urticaria, chronic urticaria, extrinsic allergic rhinitis and drug eruptions. In twenty patients with extrinsic and intrinsic bronchial asthma, only half responded, the improvement being partial, only a third of the intrinsic patients reacting at all. Atopic dermatitis was least responsive. Both drugs were given to thirty-three individuals, twenty-three of whom observed no difference, while in the remainder half preferred one drug and half preferred the other, but proportionately more patients had toxic effects from Benadryl than with Pyribenzamine, the most frequent being drowsiness, mental sluggishness, and gastrointestinal disturbance occurring in 61 per cent of the patients given the former, and in only 20 per cent of those given the latter. Other infrequent reactions were exhaustion, excitement, and dizziness. In a second report, Loveless¹⁷⁷ analyzed her own 200 patients and an additional 3600 taken from the literature. Sedation was the most common side effect following the administration of Benadryl, additional symptoms being drowsiness, inability to concentrate, mental confusion, prolonged and untimely sleep, stupor and narcolepsy. Three times as many reactions occurred with Benadryl as with Pyribenzamine, of which the most common side effects were in the gastrointestinal tract, as nausea, bad taste, anorexia, pyrosis, epigastric distress, indigestion, abdominal cramps and occasional vomiting and diarrhea. With Benadryl, some patients had wakeful excitement and others, insomnia; some, sedation, and others, irritability and nerv-

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ous tension. Common to both drugs was dizziness and vertigo, occurring in 7 per cent of those taking Benadryl and 1 per cent of those taking Pyribenzamine. The gastrointestinal symptoms occurred in 8 per cent of both groups, but in all, 46 per cent of the patients given Benadryl manifested sedation, and only 8.5 per cent of those taking Pyribenzamine. As regards the conditions treated, 75 per cent of the patients with non-seasonal rhinitis and hay fever showed improvement, which occurred in a little over half the patients with intrinsic allergic rhinitis and less than half of those with bronchial asthma, the response being least satisfactory in those with non-seasonal extrinsic bronchial asthma. Acute and chronic urticaria responded well in 80 to 95 per cent of the cases, with improvement seen in 60 per cent of those with atopic dermatitis. In a small group of cases including eczematous dermatitis and miscellaneous skin conditions, there was only 45 per cent improvement, with pruritus being relieved in 16 to 20 per cent of the cases. Application of the χ^2 Test of the author's figures shows the difference is significant in the cases suffering from intrinsic bronchial asthma only, but in any case, the analyzed figures show undesirable reactions, as noted in 61 per cent of 655 trials with Benadryl and in 21 per cent of 1905 trials with Pyribenzamine. Sedation was undoubtedly five times more common with Benadryl.

Kierland and Potter¹⁷⁸ administered Benadryl, Pyribenzamine and also Thenylene to 126 patients suffering from a number of allergic conditions, none receiving more than one drug at a time. It was felt that no statistically valid conclusions could be drawn, since different physicians administered the drugs. Drowsiness was most marked after the use of Benadryl, but also occurred with patients taking Thenylene. The clinical comparisons showed a high degree of similarity of results with the three drugs. Similarly, Blumenthal¹⁷⁹ used Benadryl, Pyribenzamine and Histadyl in 108 patients with hay fever. Of those treated with hyposensitization alone, good results were obtained respectively in sixty patients, appreciable results in thirty-two, and none in sixteen. An additional 108 patients treated with hyposensitization and the drugs reported corresponding relief in eighty-eight, twelve and eight. In sixty-two patients given 50 to 100 mg. Benadryl as needed, corresponding figures for good results were twenty-eight; for appreciable results, twelve; and for none, twenty-two. In fifty-five patients given Pyribenzamine, the figures were twenty-two, sixteen and seventeen; and for twenty-two given Histadyl, seven, eight and seven. No conclusions, therefore, could be drawn as to the efficacy of any of the drugs, although the best results were obtained with hyposensitization and a drug, compared to either injection or drug therapy alone. Bernstein¹⁸⁰ compared Benadryl, Pyribenzamine and Neo-Antergan and found the second to be the most effective with the greatest number of toxic reactions following Benadryl. Neo-Antergan apparently fell between the two. Alperstein¹⁸¹ chose patients who had experienced toxic reactions with Benadryl and Pyribenzamine and administered, instead, Chlorothen (Tagathen) and Bromothen. In all of twenty-six individuals, there was relief in fifteen to thirty minutes and no toxic reactions. The 50 mg. dose given three times a day alleviated all symptoms after one day of therapy in six, and after two to six days in the remainder. In an additional forty-seven patients suffering from pruritus, rhinitis, urticaria and eczema, who had neither received Benadryl nor Pyribenzamine, twenty-five were given Chlorothen and twenty-two Bromothen, with complete alleviation of symptoms and no toxic reactions.

Waldhoff and Gadshaw¹⁸² compared Benadryl, Decapryn, Hydtryllin (Benadryl and aminophylline), Phenergan and Pyribenzamine. In addition, some patients received Isuprel aerosol and Amphaphrene. Neo-Antergan and Trimeton were also administered; the side effects were listed as occurring in 61 per cent of the patients taking sublingual Isuprel and for the anti-histaminic agents, 56 per cent of those taking Benadryl, 45 per cent for Decapryn, 32 per cent for Trimeton and 1 per cent for Phenergan. The other drugs produced side effects in 15 to 32 per cent of the patients.

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In some cases there was temporary aggravation of the allergic symptoms. Serial blood counts and urine examinations indicated no unusual changes. The numbers of patients studied, however, did not lend themselves to statistical analysis. This is equally true for the paper by Harris¹⁸³ on the use of Benadryl, Histadyl, Hydryllin, Pyribenzamine and Compound 1695, sixty-five patients being treated successively with the drugs listed. In this group, it appears that Histadyl and Pyribenzamine were slightly more effective than Hydryllin and Benadryl, although the former was more effective in the cases of bronchial asthma associated with pollinosis. Compound 1695 was not as effective as the others. Although almost all the reports on animal experiments are purposely omitted from this clinical review, nevertheless, a paper by Winter¹⁸⁴ comparing the effects of Benadryl, Hetramine, Neo-Antergan, Phenergan, Pyribenzamine, and Compound RP 3015 on guinea pigs is worthy of study. After large doses (10 mg./kg.) of the drugs listed, the animals survived a thousand times or more of the usual lethal doses of histamine, although many of them died in a few hours of perforating gastric ulcer, presumably induced by the histamine. In a second experiment, varying doses of one of the drugs or of Pyribenzamine, Benadryl or Hetramine were injected thirty minutes before the intravenous injection of histamine dihydrochloride, 0.5 mg./kg. All of the controls died within a few minutes following histamine injection. The drugs could be listed in decreasing order of potency as Neo-Antergan, Pyribenzamine, RP 3015, Phenergan, Benadryl and Hetramine. The same order of potency was substantially established when the drugs were administered to guinea pigs who had been exposed to histamine aerosol as also in experiments with isolated intestinal strips. In acute toxicity experiments, none of the drugs was highly toxic, in doses comparable to the therapeutic dosage levels, but delayed deaths occurred, sometimes a week after a single injection in the case of Phenergan and Benadryl. The side reactions were most violent after Phenergan and least noticeable after Neo-Antergan, although RP 3015, Phenergan and Benadryl have a lower acute toxicity than Neo-Antergan, the ratio of the toxic to the effective dose being highest for this drug, the clinical qualities of which will be described below.

DECAPRYN

The animal experiments for Decapryn succinate were very competently performed by Brown and Werner,¹⁸⁵ who found it low in toxicity and a potent antagonistic agent for the bronchoconstriction, resulting from the intravenous injection of histamine in guinea pigs, antagonizing up to 200 and in some cases, 320, lethal doses of histamine. In a second communication¹⁸⁶ death from anaphylactic shock did not result in eight guinea pigs passively sensitized by injections of antipearl serum (1.0 c.c.). Toxicity studies by Thompson and Werner¹⁸⁷ showed that no chronic toxicity occurred in dogs given Decapryn succinate several times a day over a period of two months. Further studies by Snyder et al¹⁸⁸ showed that in rats, in the first twenty-four hours following intravenous administration of Decapryn (25 mg./kg.), 8 to 17 per cent was excreted in the urine.

The clinical evaluation by Brown et al¹⁸⁹ showed that small doses (6.25 to 150 mg.) four times daily gave excellent relief to sixty-two of 123 allergic patients suffering from bronchial asthma, urticaria, angioneurotic edema, atopic eczema, migraine, generalized pruritus, erythema multiforme, contact dermatitis, prurigo, and vasomotor, infectious or allergic coryza. The response was moderate in thirty-six patients, negligible in twenty-five. The majority of patients received single doses (12.5 to 25 mg.) with complete relief being experienced by 80 per cent of the patients with typical hay fever, and 85 per cent of those with urticaria and angioneurotic edema. Marked relief was obtained by 30 per cent of fifty-four patients with bronchial asthma, with moderate relief in 40 per cent of the patients, who nevertheless required larger doses. Of the twenty-three patients who experienced side reactions,

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fifteen were in the asthma group, with reactions being moderate in five of the remaining patients and severe in three. The most common complaint was drowsiness.

Feinberg and Bernstein¹⁹⁰ found the drug highly effective in inhibiting the wheal and flare reaction to histamine in man, doses of 12.5 to 50 mg. relieving sixty-two of eighty-one patients with hay fever, nineteen of thirty-four with non-seasonal vaso-motor coryza, five of six with dermatographism, and relief of some of the swelling and itching of urticaria and angioneurotic edema in six of nine. None of twenty-seven patients with bronchial asthma associated with hay fever were affected. Side reactions occurred in thirty-nine patients with sedation and sleepiness in thirty-six, nervousness in four, vertigo in four and headache in two, with epigastric pain in one. In six months' use of the drug, no serious effects were noted.

Further studies by MacQuiddy¹⁹¹ on forty-three patients with hay fever treated with Decapryl, 12.5 mg., preceding breakfast and lunch, and 25 mg. before retiring, for one to thirty-three weeks, gave good results in nineteen patients; fair for eight and poor for sixteen, with ten patients reporting drowsiness and/or nausea. Of thirteen patients treated in the same manner for asthma and hay fever, the results were good in eight, fair for four and poor for one. Of fourteen patients with asthma alone treated similarly, the results were good for four, fair for seven and poor for three, with one in each group reporting drowsiness. Of thirty-three patients with vaso-motor rhinitis only, results were good for twenty-two, fair for five, and poor for six, with two reporting drowsiness. Of ten patients with urticaria, results were good for seven and poor for three, with one with drowsiness. In ten patients with migraine, good results were seen in five, fair for one and poor for four, with three feeling nervous or drowsy. Two patients of five with eczema reported good results, with fair for two and poor for one, with one reporting drowsiness. Three patients with ocular allergy reported good results for two and fair for one.

Using Decapryl as one of nine antihistaminic agents in the treatment of pollinosis, Maietta¹⁹² found that one of three suffered drowsiness, although four of five receiving Pyribenzamine suffered drowsiness and nausea, and four of five receiving Benadryl presented the same complaint. This was equally true of four of five patients on Histadyl and five of fourteen on Thephorin, with three of six on Neo-Antergan and all of three on Tagathen. One patient taking Decapryl had numbness, and two on Histadyl complained of fatigue and insomnia.

The Council on Pharmacy for the A.M.A.¹⁹³ recommends the dosage of 12.5 mg. be given initially for adults, with subsequent average doses of 25 mg. or more as needed. The drug is recommended as a highly effective antihistaminic agent, but is listed as having a high index of sedation which sometimes precludes its use, particularly when large doses are required.

DIATRIN

Ercoli et al¹⁹⁴ described the toxicologic and antihistaminic properties of Diatrin, a relative newcomer to the field in June of 1948. The usual laboratory studies showed that the subcutaneous administration of 0.5-0.50 mg./kg. gave protection against 100 lethal doses, but did not prevent gastric ulceration which followed in five to eighteen hours. Subcutaneous or intravenous administration of 0.05 mg./kg. protected animals against lethal histamine asthma and 0.5 mg./kg. intravenously reduced or blocked histamine-induced hypotension in dogs for more than two hours. The intravenous LD₅₀ for rabbits and guinea pigs was 30 mg./kg. The pharmacology of the compound is similar to that of other antihistamine drugs. In a later communication, Chassin and Ercoli¹⁹⁵ showed that of 800 guinea pigs sensitized with two injections of horse serum, 0.1 c.c., given subcutaneously or intraperitoneally forty-eight hours apart, those who after thirteen days were re-injected intravenously with serum, 0.5 c.c., after injection with Diatrin, 5-10 mg./kg., survived, while 80 to 85 per cent of the control guinea pigs died in anaphylactic shock. Antergan, Benadryl,

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Neo-Antergan and Pyribenzamine gave similar results. Animals injected one day later went into fatal shock, the anaphylactic reaction lasting for the same length of time as the presence of the drug in the organism.

The clinical studies by Combes et al¹⁹⁶ concern eighty patients treated with Diatrin, 100 to 1,000 mg. daily, in the form of plain and enteric-coated tablets. All of nine with urticaria, two of three with neurodermatitis, three of thirty with dermatitis venenata, two of four with miscellaneous dermatoses, and one of five with penicillin urticaria, one of three with dermatitis medicamentosa, one of ten with atopic eczema, one of three with erythema multiforme, and one of nine with recurrent vesicular eruptions were completely relieved of their symptoms. Forty-three patients were not relieved, while seven obtained slight and nine moderate relief. In all, seven patients presented minor side effects, including nausea, vomiting, diarrhea, urinary frequency, and generalized burning of the skin. In only three instances was the drug discontinued because of side reactions, which were not present in those patients who received the enteric-coated tablets. In a study Kugelmass¹⁹⁷ used Diatrin and also Benadryl and Pyribenzamine; seventeen of fifty-one infants and children with gastrointestinal allergy being treated with the three drugs. Diatrin and Pyribenzamine improved the symptoms of vomiting 35 per cent, the colic, 50 per cent, and the diarrhea, 25 per cent. Benadryl was less effective. Diatrin relieved 75 to 90 per cent of the rhinorrhea, sneezing, nasal itching and nasal symptoms of 19 patients, while Benadryl relieved 65 to 85 per cent and Pyribenzamine, 70 to 88 per cent. In the treatment of seventy-two patients with vasomotor rhinitis, Diatrin was slightly more effective than the other two drugs, but at the best the patients achieved only 45 to 60 per cent relief. Each of the three drugs is reported as being effective in "primary hereditary bronchial asthma," and occasionally effective in secondary acquired asthma, while ineffective in the residual lung injury type. Diatrin was reported as the least toxic of the three drugs. Drowsiness occurred in 30 per cent of those treated with Benadryl, 22 per cent of those treated with Pyribenzamine, and 18 per cent of those treated with Diatrin. Other toxic reactions include irritability, digestive and skin disorders.

DIPARCOL

Another new antihistaminic agent, originally known as RP 2987, and used chiefly in Europe as Diparcol, has been reported upon by Gray¹⁹⁸ as improving two post-encephalitic and one senile vascular case of Parkinsonism, the patient being controlled by alternation of Diparcol and Solanaceus alkaloids. One of the patients, who was helpless and bedridden, became active after six days, maintaining her improvement for several months. Two other post-encephalitic patients, two senile vascular Parkinson patients, one patient with a head injury and one with cerebral glioma at autopsy showed no significant response. The only side effect was mental depression, for which amphetamine is recommended. Meyer and Weissenbach¹⁹⁹ reported the drug as useful in eight women with acne rosacea, who manifested a paroxysmal facial erythrosis after eating. The dose was three to seven 50 mg. tablets daily; after three to four days of treatment the congestion disappeared, and after ten days, the therapeutic effect of the drug lasted for several days or weeks. Its action facilitated other means of therapy. An interesting facet in the studies of antihistaminic agents is furnished by the work of Mahaux and Kowalewski,²⁰⁰ who administered 250 mg. of Diparcol to six patients with senile Parkinsonism and to nine patients with post encephalitic Parkinsonism and discovered that the basal metabolic rate was reduced from plus 39 to plus 15.5 in the first group, and from plus 49 to plus 11 in the second group. Extending the experiment to severely hyperthyroid patients, it was discovered that the basal metabolic rate was reduced from plus 46 to plus 14.4 in seven patients and from plus 24.5 to plus 7.7 in seventeen moderately hyperthyroid subjects, with a reduction from plus 15.9 to 2.6 in sixteen slightly hyperthyroid individuals. In normathyroid subjects, the reduction was from plus 4.9 to minus 1.4. In ten subjects with an

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average basal metabolic rate of plus 29, exercise increased the rate to plus 51.8. After 250 mg. of Diparcol, and forty-five minutes of rest, the rate was plus 15.1. At this time, a second period of exercise equal to the first increased the rate only to plus 23.3.

DRAMAMINE

Although Dramamine has antihistaminic effects, the accidental discovery that it relieved motion sickness sent explorations in the field of antihistamine therapy in a new direction. Strickland and Hahn²⁰¹ reported in April of 1949 that eighteen individuals subjected to twelve one-hour flights at 5,000 ft., conducted so as to simulate flying intermittently through moderately turbulent air 75 per cent of the time, were not air sick in seventy-seven of 108 individual flights, as compared with forty-eight of 108 flights in which placebos had been given. The Dramamine, 100 mg., was administered prophylactically. Gay and Carliner²⁰² reported that Dramamine, 100 mg., followed by the same oral dose every five hours and at bedtime to a group of soldiers prior to a ten-day voyage prevented seasickness in all but two of 134 and that the oral administration to 389 during the ten-day voyage, two to twelve hours after the onset of symptoms, completely relieved 372 within one hour following the first dose. Seventeen subjects were only partially benefited or not at all. The incidence of severe seasickness affected 195 of 881 other soldiers, 187 of whom were completely relieved within thirty minutes. The substitution of placebos for the drug when it had been effective brought a return of symptoms. No side effects were noted. This paper has been commented upon at length by Tyler,²⁰³ who points out that Drs. Carliner and Gay left themselves without adequate controls and that it cannot be determined with certainty from their paper to what extent the remission of symptoms was due to medication, change in weather, and sea conditions or to the phenomenon of adaptation. Tyler feels that on the basis of the single experiment reported upon, no convincing evidence has been presented to indicate that Dramamine is any more effective than hyoscine, 0.6 mg., in preventing motion sickness. This is further borne out by the paper by Strickland and Hahn (quoted by Tyler) in which it is reported that 55.6 per cent of the placebo group became sick. Under this moderately high sickness rate, 28.7 per cent of a like number receiving Dramamine became sick, indicating that the medication gave protection to about 50 per cent of the patients. Strickland²⁰⁴ administered Dramamine to 206 young air force men not conditioned to flight. Of these, eighteen showed dizziness, mental depression or drowsiness. Strickland, however, reports that Dramamine is an effective preventive of motion sickness.

It is only natural that Dramamine would be used for other conditions associated with nausea and vomiting. Carliner et al²⁰⁵ described its use in forty-three women to control the nausea and vomiting due to pregnancy. Of these, thirty-one were completely relieved within three hours. When a placebo was substituted, ten patients relapsed to recover when Dramamine was given. No relief was obtained in twelve patients.

Witzman²⁰⁶ reported Dramamine, 300 mg. daily, as effective in forty-three of forty-seven patients, whose chief complaint was vertigo. Two additional patients showed marked improvement and two were not helped. Some patients complained of drowsiness necessitating the reduction of the drug to 25 to 50 mg. three to four times daily. The patients who suffered from vomiting were given the drug rectally by means of a perforated capsule. One patient with a suppurative labyrinthitis secondary to cholesteatoma and a second patient with early meningitis, secondary to chronic purulent otitis media with a fistula of the horizontal canal were completely relieved of their symptoms with Dramamine therapy.

It was soon discovered that Dramamine was effective also in relieving the vestibular reaction following labyrinthine fenestration operations. Camp²⁰⁷ administered the

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drug (200 mg. rectally or orally) immediately following the operation, giving subsequent oral doses of 100 mg. at intervals of three hours for four doses on the first day and six doses on the second day. The drug markedly relieved the post-operative symptoms of eight of twenty-eight patients. Nine patients were considerably relieved, and eleven, moderately so. There were eight relapses occurring after discontinuation of the drug and all of these were successfully relieved by readministration. Only four of the twenty-eight patients suffered a severe nystagmus on the day of the operation and none had frequent vomiting. On the second postoperative day, only one suffered from moderate vertigo. Four had slight nausea, none vomited and only five presented a slight nystagmus. Almost all of the patients were out of bed by the second to fourth postoperative day, with sixteen able to tolerate a soft diet. The control patients suffered severe vertigo, nausea and nystagmus with frequent vomiting on the first day, with none able to tolerate a liquid diet until forty-eight hours postoperatively.

Dramamine was next used in radiation sickness by Beeler et al.²⁰⁸ who treated eighty-two patients with doses of 100 mg. thirty to sixty minutes before and three hours after treatment. The total dose was 200 to 400 mg. Initially, all patients experienced nausea and fifty-three vomited. With Dramamine, vomiting ceased in twenty-one in whom there was no nausea or prostration. In forty-four more patients, there was no vomiting but some nausea. Four patients had mild discomfort, while four of thirteen patients, who could not retain and absorb the drug because of vomiting, obtained slight or no relief. Twenty-three patients were used as controls, with results being reported as excellent in none, good in three, fair in nine and poor in eleven. When placebos were substituted in six patients who responded well to Dramamine, all relapsed. The side effects included drowsiness in fifteen, resulting in a voluntary discontinuation of the drug in three; eight reported a bad taste, two, paresthesias, and one, nausea. Dizziness and drowsiness also occurred in the control patients because of the x-ray therapy or the patient's poor nutritional condition.

In a letter to the editor of the J.A.M.A., Kerman²⁰⁹ reported that he had used Dramamine for nausea and vomiting following electroshock therapy, the dose being 100 mg. one hour before treatment. It was successful in fifteen consecutive cases, with no failures. Kerman also reported on eight cases of migraine treated with Dramamine, every one of whom reported benefit with the use of the drug. The only side effect was sleepiness. In a letter to the editor of the N.E.M.J., Werner²¹⁰ reported on his own Ménière's disease, present for thirteen years. With Dramamine there was a dramatic and immediate cessation of all vertigo and a 75 per cent improvement in tinnitus, with some increase in hearing of the left ear. In a third letter, Lamar²¹¹ wrote to the J.A.M.A. that he had used Dramamine in six patients, using the 100 mg. dosage, who had previously shown a severe intolerance to aureomycin, to which they responded with intense nausea and vomiting, the symptoms clearing immediately, the patients being able to tolerate 1,000 mg. of aureomycin by mouth every four hours without discomfort. The drowsiness, when present, could be controlled by coffee.

HISTADYL (THENYLENE)

Since Histadyl and Thenylene are trade names for the same compound, they are reviewed together. In 1947, Pierce and Mothersill²¹² reported on the preliminary trial in seventy-seven patients given Histadyl. The drug was found to be most effective in treating urticaria due to drugs, serum and food allergies as well as in hay fever and histamine-induced headache. It was ineffective in bronchial asthma. The side effects described include light-headedness, sleepiness and dizziness. Studies done on blood, heart, liver and kidney function show that doses of 100 to 200 mg. daily caused no evidence of chronic toxicity in the five patients subjected to laboratory tests.

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In a subsequent report, Feinberg and Bernstein²¹³ described Histadyl as a "potent antihistaminic substance," since it benefited seventy-nine of 112 patients with hay fever, forty-four of ninety-five with non-seasonal vasomotor rhinitis, seven of twelve with urticaria, seven of nine with dermatographism and also one with pruritus of unknown origin and two of three with pruritus ani. Considerable relief of itching is reported as being reported by eight of thirteen patients with atopic dermatitis. In six of nine patients suffering from pre-asthmatic spasmodic cough, the influence was favorable, although the dyspnea of thirty asthmatic patients was not relieved. Such relief as did occur lasted only two to six hours and was not complete. Although 50 mg. doses orally four times daily were well tolerated, approximately 25 per cent of the 253 patients given such doses described the side reactions as consisting chiefly of sedation, which did not equal that usually produced by Benadryl, but equalled or exceeded that produced by Pyribenzamine. Other side effects were vertigo, nervousness, oral dryness, excitation, insomnia, headache, nausea and diarrhea. As with similar drugs, Thenylene was selectively superior for particular individuals. Martins²¹⁴ reported on its use in sixty-one patients, excellent results being obtained in thirty-six of forty-four with hay fever and one with asthma; in four with urticaria, one with pruritus, one with dermatitis, and two with dermatitis venenata, as well as in six of eight patients with hay fever and asthma, the hay fever being relieved, and in one, the asthma. Martins described moderate relief as being obtained in six patients with hay fever and in three with both hay fever and asthma, with the hay fever being improved in one, and in two, the asthma. Of these patients, 57 per cent reported soporific effects, in two-thirds of whom the somnolence was relieved with Desoxyn, to such a degree that a dose of 2.5 mg. was given with each 50 mg. of Thenylene. Among the other toxic reactions described are headache, glossitis, tremor, nausea, dizziness, and dermatitis, all of which subsided when the drug was withdrawn. Similar results were obtained by Friedlaender and Friedlaender,²¹⁵ who found that symptomatic relief was afforded for several hours following each dose of the drug in cases of urticaria, hay fever and perennial allergic rhinitis. The results in asthma were not striking. The pruritus of allergic dermatoses in some instances was alleviated. Again, side effects were reported in 25 per cent of the patients, these being chiefly drowsiness, vertigo and gastrointestinal upsets, which were rarely sufficiently severe to warrant discontinuation of the medication. Saletta²¹⁶ reported excellent results with Histadyl (50 mg. three to five times daily) for hay fever, and 400 to 500 mg. daily for urticaria. The results were excellent in twenty-one cases of pollinosis and good to excellent in four cases of hives, excellent in one case of serum sickness and poor in one case of asthma. The only toxic reaction noted was a dull frontal headache lasting ten to thirty minutes in three patients. In others, the drug temporarily lowered systemic blood pressure ten to fifteen mm.

In another report, Kierland and Potter²¹⁷ used Histadyl (100 mg. three to four times daily) in seventy-eight patients with various types of dermatitis. The best response, as usual, was obtained in patients with urticaria. The other conditions treated included atopic eczema, dermatitis venenata, erythema nodosa, sensitization dermatitis due to overtreatment and mycosis fungoides. Other patients were given Benadryl or Pyribenzamine, or both. All of the drugs were equally effective in urticaria. Ten of the patients preferred Thenylene, although in twenty-two, toxic reactions necessitated withdrawal of the drug. The side reactions described include the usual drowsiness, dizziness, vomiting, headache, insomnia and nervousness, although patients intolerant to one drug could tolerate another. No cumulative effects were noted.

Epstein and Macaulay²¹⁸ described Histadyl cream (2 per cent) in the treatment of pruritic dermatoses, the drug relieving irritation of twenty-seven cases of herpes simplex chronicus, four of seven cases with mild or moderate dermatitis, six of nine cases of eczema of the hand, one of six cases of infantile eczema, one

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of two cases of nummular eczema and four of six cases of an unclassified subacute dermatitis. The itching was concurrently relieved in those patients in whom the dermatosis was unaffected. The ointment base alone was ineffective, and there were no side effects, excepting in two cases of atopic dermatitis in whom the ointment seemed to aggravate an acute flare-up. Bereston²¹⁰ found that of 104 cases of pruritic dermatoses, 40 per cent obtained relief by application of the Histadyl cream and carbowax for as long as the ointment was applied. His series included disseminated neurodermatitis, in which ten of twenty-eight patients were helped, and twenty-four cases of anal, vulval or scrotal pruritus, of whom fourteen were helped. The drug was effective in only two of nineteen patients with contact dermatitis, four of twelve patients with localized neurodermatitis, and eleven of twenty-one with eczematoid dermatitis. Fourteen patients in all, of the various groups described, improved and with the carbowax base alone. In no patient was there any toxic reaction or contact dermatitis.

The toxic reactions are delineated by Snyderman²²⁰ whose patient, a twenty months' old male child, accidentally ingested 800 mg. of Thenylene. Cyanosis, unconsciousness and convulsions appeared, to be followed by a period of cardiorespiratory depression. Normal supportive measures and a short-acting barbiturate caused improvement in twelve hours and complete recovery in twenty-four.

In view of the fact that patients taking Thenylene complained sufficiently often of nausea and epigastric distress, the use of enteric-coated tablets was employed. Hartman²²¹ administered such tablets to 107 of 112 patients who had obtained relief from the uncoated tablets, the coated tablets being effective in preventing the allergic symptoms for ninety-five patients in this group. The gastrointestinal side reactions were abolished in seventeen of the nineteen patients, who had previously responded to the uncoated tablets with nausea and vomiting. The other usual side reactions were present in sixteen of these patients. Of 206 subjects treated with the uncoated tablets, 112 had moderate to complete relief or prevention of symptoms. An increased effect of Histadyl was described by Mothersill,²²² who gave one group of patients Histadyl alone and another, Histadyl (25 mg.), with ephedrine (8 mg.). Of the patients taking the combination, 33 per cent reported complete, or almost complete, relief. Of the patients taking Histadyl alone, 15 per cent reported drowsiness, whereas of those who took the combination, only 9 per cent reported mild drowsiness.

A new use for Histadyl was described by Seelman and Miller,²²³ who described a patient with thrombophlebitis migrans of twenty-five years' duration. The patient had not responded to previous therapy, bedrest, heparin, sulfonamides and vein ligation. He was entirely relieved of any signs or symptoms of venous inflammation by 50 mg. three times daily with 100 mg. at bedtime for seven days.

HISTAPHENE

Histaphene is represented in the literature by a single preliminary note by Lambelin,²²⁴ who used the drug in fourteen patients varying from twenty-three to seventy-four years of age, who suffered from eczema, contact dermatitis, lichen planus, relapsing urticaria, prurigo, pruritus, or dyshydrosis of the hands. The results paralleled those usually obtained with the other antihistaminic agents. There was a rapid progression of the lesions in acute cases, and a lasting improvement in chronic cases. Only one patient reported drowsiness.

HYDRYLLIN

The poor effects achieved with antihistaminic agents in bronchial asthma led to the combination of Benadryl (25 mg.), and aminophylline (100 mg.) in the single compound termed Hydryllin. Segal et al²²⁵ found that there was approximately 80 per cent protection against histamine-induced bronchospasm in five patients, two hours after oral administration of two tablets. The protection lasted approximately

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five hours. In mecholyl-induced spasm there was a 40 per cent protection in six patients given such treatment, the maximum protection occurring in three hours. Brown and Brown²²⁶ administered Hydryllin as one or two tablets three or four times daily to 121 patients, noting improvement in ninety-seven. The highest degree of relief occurred in 82 per cent of the pollen and infectious asthma patients. Drowsiness or dizziness was present in 26 per cent of the patients. Other side effects include gastrointestinal disturbances, salivary duct spasm, shakiness and wheezing. In 21 per cent of the patients, the drug was discontinued because of these toxic effects. Levin and Moss²²⁷ treated twenty-two patients with bronchial asthma of the type not complicated by bronchial infection with two to nine tablets daily, reporting that four obtained 100 per cent relief and twelve, 50 to 75 per cent relief. The freedom from symptoms lasted 3-6 hours following each dose. In three additional patients with asthma complicated by infection, only one was relieved, and in twenty-three patients with seasonal hay fever, only two reported 100 per cent relief and eighteen, 50 to 75 per cent relief. In sixteen patients from all three groups there were side reactions of sleepiness, dizziness or nausea.

A comparison of Hydryllin and Trimeton was made by Manace,²²⁸ who reported 60 to 65 per cent relief of asthma in thirty-five patients with 75 per cent relief of sixteen with hay fever, and 75 per cent of twelve vasomotor rhinitis. The chief side effect was drowsiness. In patients aged six to sixty-two years, Trimeton gave 60 per cent relief to twenty-four patients with asthma, to 75 per cent of twenty with vasomotor rhinitis, and to 80 per cent of forty-six with hay fever, as well as to 70 per cent of ten with urticaria. Drowsiness was also experienced in about half the patients affected by Hydryllin.

The effect of Hydryllin on the skin was investigated by Perry et al.²²⁹ who believed that histamine iontophoresis was superior to histamine intradermal injections, scratch tests or skin temperature changes for testing histamine antagonism. Of six groups of ten subjects each, one group received placebos. Each of the other groups received Hydryllin and other antihistaminic compounds, which by this test could be ranged in the following decreasing order of activity, namely, Hydryllin, Pyribenzamine, Benadryl, ephedrine sulfate and aminophylline. Pillsbury et al²³⁰ administered two to twelve tablets of Hydryllin to 154 patients suffering from a number of skin conditions. They report the combination of Benadryl and aminophylline as being efficacious in acute and chronic urticaria, angioneurotic edema, penicillin dermatitis, dermatitis medicamentosa, with some patients with contact dermatitis and atopic eczema achieving relief. Patients with eczematous dermatitis, pruritus vulvae and ani, localized nerodermatitis, lichen planus, erythema multiforme, psoriasis, and neurotic excoriations, were not relieved. In all, approximately 20 per cent of the patients reported side reactions. Five patients apparently obtained as much relief from the placebos as from Hydryllin. The authors state, and wisely so, that much larger series of patients must be accurately evaluated before any final conclusion is reached as to the effect of the drug on exfoliative dermatitis and dermatitis herpetiformis.

Of more than passing interest is the report by Falk and Newcomer,²³¹ who describe a typical case of Loefller's syndrome, the patient being treated by penicillin in oil and wax. There were chills, fever and a cutaneous reaction with severe leg pains and violent hives at the injection site by the end of the third week. Coincident administration of Hydryllin every four hours lowered the temperature to normal, but did not relieve the leg pains. A second patient, presenting a Loefller syndrome was treated symptomatically with Pyribenzamine which was found to be as effective.

LINCOLYL

The results with Lincolyl are similar to that of Poralyl, the drug being probably about one-half as effective, weight for weight. Metzger et al²³² administered the

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drug in doses up to 75 mg. daily, with 12.5 per cent of 143 patients with allergic diseases reporting complete symptomatic relief, and 48 per cent, partial relief. In one-third of the patients, the skin histamine response decreased after one week of therapy with 600 mg. daily. Depressant effects occurred when 800 mg. was given daily for one week. In 17.2 per cent of the patients side reactions were described as drowsiness, dizziness and blurred vision, headache, confusion, fatigue and weakness, diarrhea, heartburn, dry mouth, abdominal cramps, palpitations and jumpiness.

NEO-ANTERGAN

Although the animal experimentation with Neo-Antergan is unusually detailed and complete, only selected clinical papers will be reviewed. Early in 1948, Hunter and Dunlop²³³ reported on the use of Neo-Antergan (0.1 to 0.3 gm. for children and 0.3 to 0.6 gm. for adults) administered to thirty-five patients with frequent attacks of "allergic asthma." The drug was given to alternate patients, placebos containing starch and lactose being used to treat those not receiving the drug, the procedure being reversed after three months. Eleven patients apparently improved with both Neo-Antergan and the placebos, and of these, three received further treatment with the drug, but improvement was not maintained. In four patients, the asthmatic state was definitely worse during Neo-Antergan therapy, and three patients could not be followed-up adequately. The side effects described include nausea, drowsiness and dizziness. Two months later, Herxheimer²³⁴ reported that the vital capacity had been increased in twenty-one of thirty-nine patients with bronchial asthma following Aleudrine (Isuprel) therapy, the patients receiving 0.02 to 0.06 gm. of the drug per lingually, or 1, 3, or 5 per cent solutions by inhalation. Anthisan was reported in the same study as being successful in twenty-six of thirty patients with bronchial asthma, in that it permitted them to sleep without any wheezing all night. The doses given range from 0.07 to 0.7 gm. of the drug orally, or 10 per cent of the solution used by inhalation. Tolerance did not develop in patients given the drug only once daily. Side reactions described include drowsiness, nausea and diarrhea. In a later communication, Herxheimer²³⁵ defended this conclusion that Neo-Antergan increased the vital capacity of asthmatic patients against Dunlop and Hunter, who had stated that the increase was insignificant and that tolerance to the drug did not develop. He stated that his experience indicated that increases in vital capacity, although small, were significant and that tolerance did develop, suggesting that Dunlop and Hunter had used suboptimal doses of the drug. In a third communication, Hunter²³⁶ reported on the inhalation of histamine, mecholyl or allergenic extracts, and the attacks thereby produced recorded by a spirometer. He stated that in a number of normal and asthmatic subjects, the bronchial obstruction and the bronchospasm could be effectively prevented by prophylactic Neo-Antergan or Phenergan. No protection was achieved, however, for severe attacks. He feels that the individual effective anti-histaminic substance and its dosage must be found in each case by trial and error and when so found night doses can be combined with day doses of ephedrine, while any additional acute attacks can be checked by Isuprel. The combination is stated to have been used successfully in a number of patients who had been rendered capable of regular employment.

Neo-Antergan was carefully studied by Southwell²³⁷ in twenty-five asthmatic patients and in fifteen with hay fever, the patients being of the extrinsic type with minimal infection and lung damage. Each was graded at the outset according to the severity of past symptoms, with the first grade including patients whose attack rate was less than one monthly, while the sixth grade patients were unable to work, owing to continuous wheezing. The trial lasted eight weeks, the patients being examined at the end of each week. For the first two weeks, placebo tablets were given and thereafter, true and placebo tablets were alternated at intervals of two to three weeks. The dose for Neo-Antergan for the first three days was 0.1 gm. three times

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daily, increasing subsequently to 0.3 gm. three times daily. At the end of a trial period, the average grading figures were calculated for the weeks on placebo and medicated tablets, and these were regarded as symbolic of the weekly severity of the patient's asthma. The average weekly grade numbers for the series of patients were three to six when treated and 3 to 6 when untreated (on either placebo or medicated tablets, respectively), proving Neo-Antergan of little or no value in the treatment of bronchial asthma. The figures illustrate the importance of adequate control with placebo tablets. The author states that no beneficial effect was noted in the milder cases or in those of recent onset, and the sedative effect did not benefit the asthmatic attack rate. Two patients were greatly improved by the placebo tablets. In a similar trial in hay-fever patients sensitive to grass or tree pollens, the average weekly gradings were 3.8, 3.73, and 1.5 when untreated and on dummy and real tablets, respectively. The patients who responded regarded the effects as "equal to any but the most successful desensitization course." Neo-Antergan was therefore considered of real value in the symptomatic treatment of hay fever. Twenty-three of the forty-two patients reported side effects; nausea in ten, nausea and drowsiness in six and drowsiness in four, to list some of the untoward reactions.

According to Calder,²³ of thirty-eight patients with vasomotor rhinitis, twenty-nine reported moderate to good relief of symptoms, as did six patients with hay fever taking Neo-Antergan in doses of 0.1 gm. three times daily for five days and, in the absence of untoward reactions, 0.2 gm. tablets three times daily for ten days. Reduction in dosage caused partial return of symptoms, and in this group, the incidence of untoward reactions, especially drowsiness, was very low. On the basis of treating 147 patients with hay fever, Weiss and Howard²⁴ recommended pre-seasonal or perennial hyposensitization as supplemented by 50 to 100 mg. tablets of Neo-Antergan or Pyribenzamine, three or four times daily, as required. Neo-Antergan is noted as producing a greater number of side reactions and of being slightly less active than Pyribenzamine. In perennial vasomotor rhinorrhea, Reid and Hunter²⁵ reported nineteen of thirty-five patients achieving complete relief without relapses during a six months' follow-up period, with twelve achieving some relief, and four, no relief, the dose being 0.6 gm. daily for four weeks. In some cases, 0.2 gm. daily was sufficient. Four patients required 0.8 gm. daily for complete relief. On placebo therapy, 5 per cent of the patients obtained complete relief, 35 per cent some relief and 60 per cent no relief, a total of 40 per cent being improved by placebo medication.

In this country, work by Schwartz et al²⁶ on 141 allergic patients suffering from hay fever and vasomotor rhinitis, as well as bronchial asthma, showed that over-all symptomatic relief could be obtained in eighty-seven patients, fifty-four reporting no relief. The poorest results occurred in bronchial asthma. Thirty-five patients suffered from toxic reactions, including drowsiness, nausea, diarrhea, abdominal cramps and headache, in some cases so severe that it was necessary to discontinue the drug. The patients were maintained on a 50 mg. three times daily dose, at which level 24.8 per cent showed side reactions. The best results occurred in sixty-seven of ninety-six cases of hay fever. This dropped to 59.1 per cent (thirteen of twenty-two cases) in patients with vasomotor rhinitis. Only two or fifteen patients with bronchial asthma responded.

Reid and Hunter²⁷ followed up nineteen of thirty-five patients who had been successfully treated for perennial vasomotor rhinitis with Neo-Antergan six months previously. All were still symptom-free. Of seventeen patients who had taken medication fifteen months previously, fourteen were still symptom-free, and three presented a return of symptoms. Of the seventeen, thirteen were studied as regards nasal mucosa, the type of secretion and whether eosinophilia was present in biopsy material. Two stated that they had been occasionally upset during the fifteen months' period, while the others seemed entirely well. In seven, the nasal mucosa appeared to

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be normal, while in six it was pale and moist. The nasal secretion of eleven was dry, while three had mucoid secretion. Biopsy tests were negative in eight, positive in one and borderline in four. The positive case showed a considerable eosinophilia in the biopsy material and was considered to be an allergic individual.

A larger series studied (211 cases) was reported upon by Tobias and Grindon,²⁴³ who administered Neo-Antergan in 25 to 50 mg. doses three times daily. Some patients with atopic eczema received doses of 400 mg. daily, while in acute urticaria the usual dose was 50 mg. four hourly with 100 mg. at bedtime. In acute urticaria, seven of sixteen patients were "cured," with seven improved temporarily and two showing no benefit. In chronic urticaria, four of five reported "cure" and one, no benefit. In passive urticaria the pruritus of four patients was relieved, but not of the other two, the eruptions being unaffected. In ten children with atopic eczema, five showed marked improvement, four moderate, while five patients with generalized eruptions found their pruritus relieved by Neo-Antergan. Delayed reactions occurred in adults with atopic eczema, who were not benefited, the pruritus not being diminished until the drug had been taken for at least thirty days. In two patients with an exfoliative dermatitis neither the eruption nor the pruritus was affected, nor were eleven patients with pruritus ani relieved. There were no effects in thirty-six patients with disseminated neurodermatitis, in four with nummular eczema, in four with erythema multiforme, or in two with dermatitis herpetiformis. Moderately toxic symptoms were reported in ten patients and mild side reactions in thirty-two. The side effects included nausea, dizziness, paresthesias, nervousness, insomnia, weakness, headache, cramps and heartburn. The failure of relief with oral medication may be corrected by topical application as shown in the report by Rasmussen,²⁴⁴ who treated twenty patients with pruritus ani, with Neo-Antergan cream, 2 per cent. Twelve of the patients obtained excellent results, three good results, five not being benefited. The cream was applied nightly or whenever itching was present, relief occurring within two to three minutes and lasting ten to twelve hours. In addition, the ointment relieved the symptoms of seventeen other patients suffering from pruritic dermatoses, provided the lesions were slight and situated in "delicate skin areas." It was poorly tolerated in exudative eczema. That the drug was readily absorbed was proven by the fact that for one hour afterwards its presence in the skin reduced histamine whealing induced by electrophoresis. The author, however, attributes the anti-pruritic properties to the anesthetic effect.

The miscellaneous effects of Neo-Antergan include its use in the pruritus of jaundice, as reported by Hunter and Dunlop.²⁴⁵ The dose is 0.2 gm. every four to six hours. Four patients with iodine reactions seen following bronchography or pre-operative disinfection of the skin by Boucher and Lafuma²⁴⁶ were similarly relieved. The drug has also been used in the management of liver and insulin sensitivity by Hunter and Hill.²⁴⁷ Five of nine cases required 300 mg. one hour before the injection, following which two patients had no reactions, two a modified reaction and one a severe reaction. In four additional patients, two of whom reacted severely, 1 gm. of Anthisan given twenty-four hours before the liver injection resulted in one patient showing a mild reaction and three being free of symptoms. One patient, severely sensitive to insulin, was relieved after four days of treatment, the dose varying from 500 to 800 mg. daily. An additional two mild reactors, with local lesions were cured, after a ten-day course. The authors suggest wisely that the drugs should be given for longer periods of time to enable spontaneous desensitization to insulin to take place.

Brown et al²⁴⁸ used Neo-Antergan in radiation sickness. Their negative report showed that doses of 0.6 gm. daily did not prevent the appearance of the condition in sixteen of seventeen patients, treatment being instituted five days before post-operative roentgen irradiation for breast carcinoma. The administration had to be discontinued in many patients because of severe constitutional reactions. In five

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patients, an erythema developed which disappeared upon withdrawal of the drug. On the other hand, in motion sickness, fifty-one of 131 seasick individuals given Neo-Antergan, 100 mg., and Hyoscine 1/100 gr., alternately, preferred the Neo-Antergan, while forty-two individuals preferred the Hyoscine. McEvedy,²⁴⁹ on the basis of these studies, recommends Neo-Antergan, one tablet three times daily. In this regard, the notes of Tyler (*op. cit.*) regarding Dramamine should be noted. The comparison of Hyoscine, Dramamine, and Phenergan with Neo-Antergan was done by Beaumont.²⁵⁰ Of his 100 patients, 20 per cent had failed to respond to Hyoscine and 7 per cent to Dramamine. Neo-Antergan by suppository and orally relieved these patients whose average duration of vomiting prior to medication was thirty-six hours. Following the Neo-Antergan, Phenergan was given in doses of 25 mg. No untoward reactions, excepting drowsiness, occurred. The author makes no mention of the fact that seasickness is a self-limiting condition, the patients and the control individuals all acquiring their "sea legs" within a comparatively short period of time.

Dougray²⁵¹ treated ninety-four pregnant patients who complained of nausea and/or vomiting, with Neo-Antergan, two to seven tablets daily, or 0.025 gm. Phenergan, three times daily. Twelve were unchanged, four were improved and seventy-eight reported cure. One thirty-four-year-old patient who had suffered from intense continual vomiting during the tenth week of pregnancy, no response having been noted to phenobarbital, vitamin B-1, intravenous glucose saline, or glucose by mouth, responded to Phenergan and Neo-Antergan given on the first, third and tenth days of hospitalization, the dose of Phenergan being one tablet morning and night initially, increased gradually to seven tablets daily. Anthisan was used in doses of 0.1 gm. three times daily. Drowsiness appeared at the top dose of Phenergan, requiring amphetamine sulfate (5 mg.) each morning, the drowsiness being the chief side effect of both drugs in almost all patients.

On the basis that acute nephritis might be an allergic response to bacterial toxins, Craig et al²⁵² administered Neo-Antergan (0.1 gm. three times daily) to eight children, aged two to nine years. By the eighth day, two children, in whom the condition had been mild, the symptoms being hematuria, albuminuria and puffiness around the eyes, were noted as cured, while six more patients with more marked urinary pathology, including increased blood urea, azotemia, marked edema, hypertension, and hypertensive convulsions, were cured in about fifteen days. One patient relapsed, requiring the readministration of 0.1 gm. every four hours to produce a complete cure in ten days. Three control individuals with a milder form of nephritis and six with moderate or severe symptoms not treated with Neo-Antergan were cured on an average of twenty-one and 128 days, respectively. All of the patients in either group who showed signs of active infections received penicillin or sulfonamides, although the nephrotic symptoms were not altered by the administration of these drugs. In a later report, Clark²⁵³ described eight patients with nephritis, including two with hypertensive convulsions treated for five to forty-five days with Neo-Antergan (0.3 to 0.5 gm. daily.) Full recovery was seen in six to twenty-one days, the average being thirteen days, while that for six control patients was ninety-two days.

To add to the confusion regarding "cold cures," Paton et al²⁵⁴ gave twelve subjects, who had developed colds in the preceding twenty-four hours, Neo-Antergan (100 mg. three times daily) for two days. Four reported improvement, one was unchanged and one was undecided. The average duration of the cold was 6.5 days. Ten additional patients were given placebos. Of these, four claimed to be improved, four unchanged and two undecided. For the second group the average duration of colds was 6.2 days. The clinical conditions of both patients were so similar that the examiner could not decide which patient had been given the drug and which the placebo.

Among other miscellaneous conditions treated with Neo-Antergan, are two cases of Stevens-Johnson syndrome by Salomon,²⁵⁵ the milder case showing complete re-

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covery after three days of 50 mg. doses four times daily, while the more severely ill Neo-Antergan by Horngsäbberger.²⁵⁶ Two fatalities due to Neo-Antergan have recently been reported, the first by Tobias,²⁵⁷ whose patient, a twenty-one month's old child, swallowed 600 mg. The second is by Jauhimes²⁵⁸ and is reported only by title in the Swiss literature, the original paper not having been examined. A third case is known to the present author,

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in only 9 per cent of 100 patients on the 50 mg. dose, and 15 per cent of forty-eight patients taking 100 mg. No blood pressure, blood or urine changes were noted in eight patients who took the drug three times daily for four to six months. Similar clinical results were reported by Waldbott and Borden,²⁶¹ who used the drug in 279 patients, reporting good results in ninety-one, and some improvement in eighty-two. The patients presented conditions as varied as allergic conjunctivitis, allergic rhinitis and hay fever, migraine, urticaria, atopic dermatitis, contact dermatitis and bronchial asthma. The best results were obtained in allergic nasal disease and urticaria, twenty-nine patients complaining of dizziness and drowsiness about one hour after a 50 mg. dose. Several patients presented muscular twitching in twenty minutes.

Aaron and Criepp²⁶² not only experimented with guinea pigs, but also did toxicity studies on seventeen patients, who were given Neohetramine (300 mg. daily), while thirty-seven patients were given the same dose of Thephorin, each for four days. One patient, seventy years of age, with heart failure, showed an inversion of T waves in lead C-V4, which reverted to normal upon withdrawal of the drug and on readministration again became inverted. Another patient, who took Thephorin, showed an inverted T wave during its administration, the wave becoming upright after the medication had been discontinued. No other patients showed any electrocardiographic changes. Whealing responses with ragweed and histamine were inhibited by Neohetramine, Thephorin, or Pyribenzamine, (200 mg.) given one hour orally before the test. Side reactions occurred in 23 per cent of the patients taking Thephorin and 10 per cent of those taking Neohetramine, nervousness and nausea predominating. There was some insomnia. The results are recorded as good in allergic rhinitis, either perennial or seasonal, and in urticaria and angioneurotic edema. The drug was of some value in the management of asthma, atopic and contact dermatitis. In a later communication, Criepp and Aaron²⁶³ reported on 243 children and adults suffering from hay fever, allergic rhinitis and urticaria. Two hundred and thirty-two infants were given Neohetramine elixir (25 to 50 mg.) every four hours. Of these, twenty-eight of sixty-one with allergic rhinitis, twenty-five of forty-seven with hay fever, twelve of twenty-two with urticaria and angioneurotic edema, and six of sixty-six with bronchial asthma were relieved, as were three of twenty-one with atopic eczema, one of nine with contact dermatitis, three of three with physical allergy. Three patients with gastrointestinal allergy were not affected. Side reactions occurred in eighteen patients and consisted of the usual restlessness, insomnia, constipation, rhinorrhea, drowsiness and headache.

In a report by Schwartz and Reicher,²⁶⁴ the dose was 50 mg. one to four times daily with occasional patients taking 100 mg. three to four times daily. Relief of symptoms was seen in thirty-eight of fifty-three patients with hay fever, fourteen of twenty-two with vasomotor rhinitis, ten to twenty-four with bronchial asthma, three of five with chronic urticaria, one of six with atopic eczema and one case of pruritus (unspecified.) Mild reactions were noted as occurring in 17.2 per cent of these patients. In a later report, Schwartz²⁶⁵ compared the side effects of Neohetramine with those seen following Antistine, Benadryl, Histadyl, Neo-Antergan and Pyribenzamine, the successive number of cases being 97, 217, 89, 141 and 126, with eleven patients receiving Neohetramine. Although these numbers are not significant and not comparable, the percentage of side reactions are given, respectively, as 22.7 per cent, 61.3 per cent, 20 per cent, 24.8 per cent, and 35.7 per cent. Those for Neohetramine were 7.2 per cent (as stated above, of eleven patients.) In a third report by Criepp and Aaron,²⁶⁶ 72 per cent of 124 patients with hay fever, 80 per cent of forty-one with allergic rhinitis, 63 per cent of thirty-three with bronchial asthma, 82 per cent of eleven with atopic dermatitis, 75 per cent of twenty with urticaria, and 83 per cent of six with migraine had moderate to complete relief from Neohetramine (50 mg. every four hours.) All of the patients with contact dermatitis were helped. Ten per cent of the patients complained of side reactions, including dizziness, dia-

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rhea, constipation, headache, nervousness, nausea and insomnia. The side reactions were fewer than those caused by Pyribenzamine or Benadryl. The Neohetramine was considered slightly more active than Benadryl, but not as active as Antergan. The vital capacity improved 25 per cent or more in seven of twenty-one patients with various types of bronchial asthma following doses of 50 mg. Eight improved clinically and seven of these presented increased vital capacity, which totalled 79 per cent in one patient.

Neohetramine, of course, received its greatest publicity in its use for the treatment of the common cold. Tehrock and Mitchell²⁶⁰ treated 1,000 subjects prophylactically with Neohetramine (Anahist), 25 mg. being given four times daily throughout the season. They stated that the tablet prevented the occurrence of the common cold in a large percentage of persons who ordinarily would have suffered one or more colds. In patients who took the drug promptly within the first twenty-four to forty-eight hours, the drug either aborted the cold or stopped the progression of symptoms to a point where there was no longer acute discomfort, the individuals remaining on the job without exposing others to their ailment. In a study by Arminio and Sweet,²⁷⁰ 100 subjects were treated for 180 days, with Neohetramine (50 mg.), once, twice or three times daily. The respective numbers free of cold symptoms of each group were eighty-three, ninety and ninety-two. Of those who suffered with colds, five, seven, and six, respectively, had only the first phase, lasting twenty-four hours. None in the first group, none in the second group and one in the third group who took the Neohetramine three times daily suffered the first and second phases of the cold, lasting forty-eight hours, and twelve, three, and one suffered all three phases of colds, lasting three to seven days. In a control group of 300 patients given placebos, fifty-nine were free of cold symptoms; none suffered the first phase alone, sixty-two suffered from the first and second phases, and 179 had all three phases with malaise, cough and purulent discharge. Of the cold group, eleven developed complications such as pneumonia, bronchitis, and sinusitis. The average duration of colds among forty patients treated with Neohetramine three times daily for three days, starting during the first phase of the cold, was 1.2 days. Of forty-six individuals starting during the second phase, the average was 2.8 days; and among eighteen, whose treatment was started during the third phase, the duration was 5.1 days. Reactions were mild, nine of the 100 patients taking the drug three times daily complaining of dryness of the throat and sneezing, and two of mild nausea. All symptoms were alleviated by decreasing the dosage to 50 mg. daily. Needless to say, no such results have been achieved by other physicians treating colds prophylactically or therapeutically, and, again, time alone can give the true picture of the use of these drugs in common colds.

The last report is that of Judd and Henderson,²⁷¹ who considered the inflammatory reaction characteristic of tuberculosis as due to allergic causes, and administered Neohetramine for periods up to seven months to thirty patients with tuberculosis. Improvement was noted by x-ray as well as clinically, the coughing and expectoration decreasing with the patient's appetite and weight increasing. On early discontinuation of the drug there was a mild progression of lesions and a general recrudescence.

PERAZIL.

The first work on the pharmacological qualities of Perazil on humans by Jaros et al²⁷² dealt with its long-lasting effects. Thirty subjects, sixteen allergic and fourteen non-allergic, were scratch-tested with histamine solutions 1:4000 to 1:512,000; fifteen received Pyribenzamine (100 mg.) and fifteen, Perazil in the same dose. After a suitable recovery period the tests were repeated, excepting that the patients who received Perazil now received Pyribenzamine and vice versa. In one test with the 1:256,000 dilution of histamine, the wheals returned in fourteen of fifteen patients given Pyribenzamine within four hours, while only two of fifteen patients given

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Perazil had similar wheals, the effects of the latter in some patients lasting about thirty-two hours longer. In a cross over experiment, four of fifteen patients treated with Perazil had wheals 0.5 to 2 mm. in diameter, while thirteen of fifteen given Pyribenzamine had wheals 0.5 to 2.5 mm. in diameter. Sixty-three doses of Perazil were followed on seventeen occasions with drowsiness, while twenty-four of fifty-six doses of Pyribenzamine caused somnolence, the reactions following Perazil being much milder. Blood pressure studies on three of the subjects showed no significant changes on doses of 400 mg. In a second communication, Jaro²⁷¹ reported on the complete relief achieved after one dose on twenty-two of twenty-three patients with hay fever, eight of eight with atopic dermatitis, eighteen of twenty-one with vasomotor rhinitis and six of six with acute urticaria. The good effects lasted twenty-four hours. Three of three patients with contact dermatitis, two of thirteen with bronchial asthma, two of two with sinusitis, one of one with chronic urticaria and six of seven with other allergies obtained excellent relief. Moderate improvement was seen in eight patients with bronchial asthma and two with vasomotor rhinitis and one with hay fever, while the remainder were not improved. The greatest relief was seen in patients given the combined hyposensitization and Perazil treatment. Side effects, which were mild, occurred in only four patients, who were drowsy. Two patients, suffering from severe serum sickness reactions due to penicillin and reacting toxically to other antihistaminic agents, were treated with Perazil, the first for seven days and the second, for sixteen hours, with marked relief.

The pharmacological studies on animals by Castillo et al²⁷⁴ were interesting in that they showed Perazil to be four times more antihistaminic than Benadryl, as tested by the isolated guinea pig tracheal chain, the drug being compared with Benadryl, Tagatene, Neo-Antergan, Thenylene, and Pyribenzamine. For comparative purposes, the intraperitoneal LD₅₀ of Perazil in mice was found to be 137 mg./kg., while that for Neo-Antergan was 115, Tagatene 105, Thenylene 77, Pyribenzamine 67 and Benadryl 69 mg./kg., respectively. The chronic toxicity of Perazil in rats and dogs was extremely low. The monochloride compound (AII 289 Abbott) was shown to be equal in effect by Roth et al²⁷⁵ 50 mg. doses given orally causing marked reduction in the histamine flare in 9 human subjects for as long as twenty-four hours, while the protection afforded by Thenylene and Pyribenzamine lasted only eight hours.

The clinical evaluation by Brown et al²⁷⁶ concerned 186 patients treated with doses of 12.5 to 200 mg. daily. Of these, seventy-five had hay fever, seven vasomotor coryza, fifteen urticaria, seven intrinsic bronchial asthma, eight atopic eczema, two vernal conjunctivitis, one dermatitis herpetiformis, two psoriasis, one generalized pruritus, fourteen contact dermatitis, eighteen bronchial asthma and atopic dermatitis, thirty hay fever and bronchial asthma and one hay fever and poison ivy. Others suffered from miscellaneous syndromes, such as a combination of the above. Side reactions were seen in only five of seventy-five patients with hay fever, in one of thirteen with urticaria, in three of thirty suffering from hay fever and bronchial asthma and one of eighteen with bronchial asthma alone, usually being associated with doses in excess of 100 mg. daily. Although the results were not given in percentages they were much better than those achieved by any other antihistaminic agent so far studied by the same group of physicians.

PHENERGAN

In 1946, Halpern and Ducrot²⁷⁷ published a preliminary note on a new chemical series possessing a powerful antihistaminic and anti-allergic effect, namely, the derivatives of Thiodiphenylamine. These differed from Antergan and Neo-Antergan, which are, respectively, derivatives of aniline and pyridine. The new drug, Phenergan, was said to be less toxic than Neo-Antergan in mice and have a more powerful antihistaminic effect, inasmuch as equivalent doses of Neo-Antergan and Phenergan

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protected guinea pigs against only eighty lethal doses of histamine as against 1,500 lethal doses. The drug was described as more specific, inasmuch as there was no antagonism to acetylcholine. In six cases of urticaria, resistant to other drugs, the results were excellent, and there were no gastric disturbances or alteration of the blood picture over a period of six weeks. The only side reaction was somnolence. The dose was smaller than that employed with previous drugs, the initial dose being 0.25 gm. given in five equally spaced doses, preferably after meals. The pruritus was described as disappearing in thirty minutes and the eruption within an hour. In two cases of angioneurotic edema and one case of eczema, similar satisfactory results were observed. In a later communication, Halpern et al²⁷⁸ showed that, in animals, Phenergan was two to three times as effective as regards duration of protection, as were either Antergan or Neo-Antergan. Like other antihistaminic agents, however, Phenergan failed to modify the action of histamine on gastric, pancreatic or salivary secretions and although the animals were protected against 1,500 lethal doses of histamine, nevertheless some developed gastric ulcers, which in some cases, fatally perforated the peritoneum within twenty-four hours. In 1947, Halpern²⁷⁹ reported that the antihistaminic action of Phenergan was forty times that of Antergan, and its anti-anaphylactic action five times as great. Its effect lasted for about nine hours as compared to larger doses of Antergan and Neo-Antergan which lasted for not more than three to four hours.

In the clinical results by Vallery-Radot et al,²⁸⁰ all but one case of urticaria responded, as did three cases of urticaria due to serum sickness. Disappearance of symptoms was observed in six to eight cases with angioneurotic edema, and in thirty-six of thirty-eight cases of hay fever. In twenty-one cases of asthma, however, there was no improvement in ten and appreciable relief in seven, with complete disappearance of all symptoms in four. There was no effect in three cases of spasmodic cough, or in five cases of acute eczema. Petechiae, occurring for several weeks, ceased to appear when Phenergan was administered. Four of ten cases of migraine were favorably improved. The cases in which Phenergan failed did not respond to other forms of antihistaminic treatment. There were doubtful or no effects in cases of chronic or subacute rheumatism, infectious arthritis, and tuberculosis. The side reactions, namely somnolence, sometimes accompanied by unsteadiness, vertigo and clouding of the consciousness, are said to disappear after the first few days if treatment is continued with the same dosage, benzedrine being given simultaneously to prevent the reaction. The authors felt that the properties of Phenergan were not entirely explicable on the basis of its antihistamine qualities. Although Gate and Pellerat²⁸¹ were able to confirm the efficacy of Phenergan, stating its activity and duration were superior to those of the former products available, they observed that other drugs were preferable because of superior tolerability.

Hunter²⁸² discussing the clinical use of antihistaminic substances stated that the incidence of toxic effects was much greater with Phenergan than with Neo-Antergan, although Benadryl might be more effective for the relief of itching. He found, however, that ideal treatment consisted of desensitization in addition to the use of antihistaminic drugs, the combined treatment producing 95 per cent relief in the cases studied. Of particular interest is the fact that placebo tablets gave some relief for 34 per cent of a group of patients suffering from perennial rhinitis, Neo-Antergan producing complete relief in 50 per cent. Halpern and Hamburger²⁸³ presented some of the same data in another communication, doses of 20 mg. daily resulting in the disappearance of pruritus and urticaria within thirty minutes to three hours in seven cases of serum sickness, and of joint pains in two of four patients. There was immediate improvement in 108 of 123 cases of urticaria, in all of whom Neo-Antergan had failed to relieve the symptoms. There was improvement in sixteen of ninety cases of true angioneurotic edema, and complete relief in nine allergic of seventy-two patients with asthma, with some improvement in twenty-one non-allergic patients and

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no results in forty-two others. There was "vast improvement" in twelve of eighteen cases of prurigo and complete relief in ninety-eight of 123 cases of hay fever, with partial relief in thirty-one. None of seventeen patients with chronic eczema were completely cured, but three of twenty-two cases of acute and contact dermatitis improved rapidly to a complete cure, while others slowly improved. None of three arsenical and one gold *erythrodermia* patient, as well as others with spasmodic cough, or chronic or subacute rheumatism, were helped. In two patients there was a slight neutropenia and 25 per cent of the patients experienced slight drowsiness, vertigo and instability when standing, including a sensation of drunkenness and decrease in intellectual powers. In a brief report, Vallery-Radot²⁸¹ reported that in 180 of 200 patients, symptoms of hay fever disappeared almost immediately following the administration of 25 to 50 mg. of Phenergan. Results were less favorable in sixteen patients. There were no effects in four.

Moindrot²⁸² described the effects of Phenergan on fifty-seven patients, nine of whom suffered from acute and six of chronic urticaria, four of angioneurotic edema, eight of acute and seven of chronic eczema, with seven additional patients presenting superimposed bacterial infections, eight of generalized and five of local pruritus, and three of herpes zoster. The report states that it has a favorable influence and occasionally cures eczematiform dermatitis of external origin, the itching being diminished or suppressed. The pain of herpes is diminished and the cutaneous evolution is modified. The author considers Phenergan most promising for the treatment of herpes. The drug is stated to cause less gastric irritation than Antergan and its derivatives, and side effects are reported as rare. The ointed Phenergan gave good results when applied locally in three cases of urticaria following serum treatment. It was ineffective or irritating in three cases of eczematous pruritus and three of vulvar pruritus.

For those physicians who may be puzzled by the fact that the number of communications by Halpern is great, it should be pointed out that the same material was evidently presented to a number of journals, all of whom accepted it, including the *Journal of Allergy*,²⁷⁹ the *Bulletin of the New York Academy of Medicine*,²⁸⁰ and the *Journal of the Canadian Medical Association*.²⁸¹ Other references are therefore omitted for reasons of space, since the clinical material is almost identical.

Phenergan and Anthisan were compared by Bain et al.²⁸⁷ They discovered Phenergan to be about seven times as active as measured by the reduction of the wheal area for intradermal injections of 10, 1, and 0.1 mg. of histamine given before and at intervals after the injection of the drug. The average times for maximum action of the drug were 120 minutes for 150 mg. of Anthisan and 190 minutes for 25 mg. of Phenergan, while 50 per cent of the activity was still present 430 and 1,360 minutes, respectively. Twenty patients with chronic urticaria treated with Anthisan (300 to 1,200 mg. daily) for one to twenty-four weeks were given Phenergan (25 to 100 mg. daily) for one to thirteen weeks. Anthisan was necessary in three or four-times daily doses, while Phenergan was effective in all patients in a single nightly dose. Phenergan produced mild morning sleepiness in five patients, while Anthisan produced persistent sleepiness, light-headedness, and gastrointestinal disturbances in four patients; fourteen of the twenty patients preferred Phenergan to Anthisan, five had no preference and one preferred Anthisan. On a daily dosage basis, Phenergan was found to be fourteen times more active.

In this country Shulman²⁸⁸ chose patients who had previously been unsuccessfully treated with other antihistaminic agents and gave a single dose of Phenergan (6.5 to 25 mg. daily) after the last meal. Nine of twenty subjects with perennial vasomotor rhinitis, seven of ten with perennial and seasonal asthma, eight of eight with urticaria, two of four with eczema, three of nine with contact dermatitis and two of four with migraine had good or marked improvement. Seventeen patients complained of dizziness and one of such severe drowsiness that the drug had to be dis-

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continued. Herxheimer²⁸⁹ discovered that in patients with bronchial asthma, the optimum doses for Anthisan were 300 to 500 mg. daily, while with Phenergan and Benadryl, the necessary doses were 50 to 75 mg. Although Phenergan caused drowsiness in some cases, some patients also complained of insomnia. An intravenous injection of 25 mg. was beneficial in thirteen patients with genuine asthma and in four in whom bronchospasm was induced by inhalation or mixed inhalants or mixed pol-lens. In two normal subjects, in whom the vital capacity was reduced by the inhalation of acetyl-b-methychooline chloride (2.5 per cent) for three to four minutes there was no benefit accorded by the previous oral administration of Phenergan (25 to 50 mg.), but one normal subject obtained almost normal capacity in less than a minute when Pyribenzamine (1.5 per cent) solution was inhaled for two minutes following the choline chloride induced spasm. In normal subjects, oral Phenergan suppressed or minimized the slight subjective symptoms induced by the inhalation of histamine (3 to 10 per cent) aerosol, although the vital capacity was unchanged.

Salva and Badell²⁹⁰ used Phenergan (25 mg. daily) in the treatment of radiation sickness. On five patients who took the drug during a second period of irradiation, there were no symptoms of intolerance. An additional twelve patients, who during the first course of a period of irradiation had shown symptoms of radiation sickness were also treated. In each instance, the patient was able to complete the full course without any symptoms of intolerance. In one patient, in whom there was marked edema of the cheeks and eyelids and dermatitis of the malar region, the administration of Phenergan (25 mg. daily) caused the lesions to dry and the edema to diminish within twenty-four hours, a complete cure occurring in five days. The causal relationship in this case might well be questioned since there was no possibility of control studies being done and no way of knowing how long the edema would have lasted without treatment.

An indication of how Phenergan may act on the nervous system is reported by Sigwald.²⁹¹ The intravenous injection of Phenergan abolished the spasm and clonus and normalized the tendon reflexes of four patients with pyramidal syndromes, but failed to influence the paralysis and the Babinski and automatic medullary reflexes. Of interest also is the report by Warin,²⁹² who discovered on observing twenty patients for six to nine months that the tolerance to Phenergan did not develop as judged by the histamine-wheal test. By prescribing the drug in one dose at night, urticaria was completely controlled, with no side effects being observed on the following day.

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(To be continued in the July-August issue.)

IDIOBLAPTIC TOBACCO SENSITIVITY

(Continued from Page 395)

order to discover food or other inhalant allergens which may then become manifest by a rise in the pulse rate.

235 West Pueblo Street

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News Items

CHICAGO SOCIETY OF ALLERGY

The new officers for the Chicago Society of Allergy elected May 15 are: President, Townsend B. Friedman, M.D.; President-elect, Theron G. Randolph, M.D.; Secretary-treasurer, Milton M. Mosko, M.D.

CALIFORNIA SOCIETY OF ALLERGY

At the annual meeting of the California Society of Allergy, held in San Diego, May 1, 1950, the following officers were elected for 1950: President, Frank G. Crandall, Jr., M.D.; President-elect, Samuel H. Hurwitz, M.D.; Secretary-treasurer, M. Coleman Harris, M.D.

LOUISIANA ALLERGY SOCIETY

At a meeting of the Louisiana Allergy Society at the Heidelberg Hotel in Baton Rouge, April 26, new officers were elected. A roundtable discussion on bronchial asthma was held, with Dr. B. G. Efron as moderator. The panel discussion on "The Present Status of Antihistaminic Drugs" was led by Dr. Vincent J. Derbes. The newly elected officers are: President, H. Whitney Boggs, M.D.; Vice President, Vincent J. Derbes, M.D.; and Secretary, B. G. Efron, M.D.

BRAZILIAN SOCIETY OF ALLERGY

At the meeting of the General Assembly of the Brazilian Society of Allergy on December 29, the new directorate was elected. The new Board of Directors for 1950 is as follows: President, Dr. Nelson Passarelli (re-elected); Vice President, Dr. Eleuterio Brum Negrerios (re-elected); First Secretary, Dr. Haroldo Cardoso de Castro; Second Secretary, Dr. Newton Guimares; Treasurer, Dr. A. N. Sayao Lobato (re-elected); Librarian, Dr. Mario Miranda. Members of the Fiscal Council are Drs. Paulo Dias da Costa, A de Lima, and U. Fabina Alves, Ernesto Mendes, and J. B. Greco.

MEDICAL ILLUSTRATORS' DIRECTORY AVAILABLE

The Directory issue of *Graphics*, the official publication of the Association of Medical Illustrators, contains the name, address, training, professional experience, and reference to major published work of each member. Other information pertaining to the profession is included.

The journal, which was issued on June 1, is available to those requiring medical illustration service, and will be sent free of charge upon request to the Editor, Miss Helen Lorraine, 5212 Sylvan Road, Richmond 25, Virginia.

NEW YORK ALLERGY SOCIETY

The New York Allergy Society, New York Academy of Medicine, held its meeting on April 12. Six papers were read: Foreign Body Simulating Asthma, by Dr. Nathan Ravin; Pollen Studies at Ambrose Lightship, by Drs. Richard Wiseman and Israel Glazer; A New Approach to Mold Surveys, by Dr. Nathan Schaffer; Pollenosis with Negative Cutaneous Tests, by Dr. Murray Peshkin; New Antibiotics in the Treatment of Vasomotor Rhinitis, by Dr. Artell Johnson; and The Importance of Foods in Allergic Patients, by Drs. Harry Leibowitz, Alexander Chester, and Harry Markow.

NEWS ITEMS

BRAZILIAN SOCIETY FOR THE HISTORY OF MEDICINE

The Brazilian Society for the History of Medicine held its opening session April 19 in the Noble Auditorium of the General Polyclinic in Rio de Janeiro with the following program: Reception of the Corresponding Member, Dr. Erich Gruen, with the address of greeting by the official speaker, Dr. Jayme de Mendonca Castro; "Medical Historical Profiles" by Dr. Erich Gruen; and "Activities of the Institute in the History of Medicine of the City of Pernambuco" by Prof. E. M. Salles Cunha. Plans were made for Brazilian representatives at the Sixth International Convention of the History of the Sciences and the Twelfth International Convention of the History of Medicine, August 14-20, 1950, in Amsterdam, Holland. Preparation was also made for the First Brazilian Convention of the History of Medicine to be held in July, 1951, in Rio de Janeiro.

FIRST INTERNATIONAL CONGRESS ON ALLERGY

Plans are maturing rapidly for the first International Congress of The International Association of Allergists at Zurich, Switzerland, September 23-29, 1951. The two national allergy societies in the United States who are official members of the I.A.A. are The American College of Allergists and The American Society of Ophthalmologic and Otolaryngologic Allergy. With sixteen of the twenty-four known existing allergy societies in the world belonging to the I.A.A., and with individual fellowships representing nearly all countries, a very excellent attendance is anticipated. The members of the Organizational and Program Committees are:

President of the Congress: Prof. C. W. Loeffler, Zurich

General Secretary of the Congress: Prof. A. Grumbach, Zurich

Executive Secretary of the Congress: Dr. F. W. Wittich, Minneapolis

Members: Dr. Paul Kallös, Helsingborg

Prof. R. Meier, Basel

Prof. A. Stoll, Basel

Membership in The International Association of Allergists consists of physicians, scientists, and other professional persons qualified in allergy or those scientists representing the basic sciences from which our knowledge of allergy originates. Application blanks for fellowship or associate fellowship may be obtained by writing to the Chairman of the Executive Committee, 424 La Salle Building, Minneapolis, Minnesota.

The official languages of the Congress are English, French, Spanish, and German. The account of the session, including the papers presented and a summary of the discussion, will be edited and published as the official proceedings of the Congress. The official publication of the I.A.A. is the *International Archives of Allergy and Applied Immunology*. The subscription price is about \$7.00, U. S. money. Those wishing to subscribe can order directly from the publisher, Zurich, or from the Interscience Publishers, 215 Fourth Avenue, New York City, or from headquarters, 424 La Salle Building, Minneapolis.

The International Association of Allergists is an official member of the Council for the Co-ordination of International Congresses of Medical Sciences, which has received pledges from UNESCO "to give full support and material assistance to the Council, whose aims coincide so well with those of UNESCO and WHO."

The program, as outlined in *La Presse Medicale*, Paris, February 4, 1950, is as follows:

Topics for Discussion:

I. Diseases due to allergies; their nature and social significance

 A. Diseases due to allergies and diseases accompanied by sensitization phenomena

NEWS ITEMS

- B. Social importance of diseases due to allergies
- C. Geographical distribution of diseases due to allergies

II. Historical study of allergic damages

III. Chemical and serological studies of allergies

- A. Fundamental principles of the chemistry of antigens
- B. Antigenic function of haptens
- C. Location of the formation of antibodies
- D. Biological significance of complete and incomplete antibodies
- E. Pathogeny of allergic reactions

IV. Influence of constitution and heredity in the appearance of allergic diseases

V. Pharmacology of allergic reactions

- A. Chemical constitution and physiological reactions
- B. Success of the antihistaminic therapy
- C. Behavior of sympathicolytic substances in allergy

VI. Diagnosis of allergic diseases

- A. Standardization of the allergens
- B. Interpretation of allergic reaction
- C. Value of the functional examination of the lungs for the diagnosis of allergic conditions
- D. Psychomatic conditions in allergic diseases

VII. Study of allergies: past and future

Outstanding scientists in Europe and the Americas will participate. The American Express Company has been appointed as the official travel agency for the Congress. The average time for the trip has been planned for two months, although shorter itineraries can be arranged to suit the individual. It is important that the chairman of the executive committee get as early as possible an approximate number of those who attend from North and South America. Plans are being made to have the majority travel to Europe and return by boat, leaving from New York City. Arrangements are also being made with Pan-American Air Lines for reservations for those traveling by plane. Because competition is so great, transportation lines will rarely issue a one-way ticket, so that it is understood that a person who travels by plane will return by plane, and those who travel by boat will return by boat. All those planning to attend are urged to register their names at 424 La Salle Building, and then they will receive a prospectus containing detailed information about the Congress.

* * * *

The many friends in the allergy world will grieve to learn of the death of Dr. J. H. Frazer, former medical director of the Arlington Chemical Company, Yonkers, New York, after a protracted illness. His many friends in the College extend their sincere sympathy to his wife, residing at 146 West 79th Street, New York 24, New York. In his numerous contacts with physicians all over the country, Doctor Frazer was instrumental in arousing interest in allergy and having them apply allergy to their practice.

BOOK REVIEWS

THE MANAGEMENT OF THE PATIENT WITH SEVERE BRONCHIAL ASTHMA. By Maurice S. Segal, M.D., Assistant Professor in Medicine, Tufts College Medical School, Boston. 158 pages, with figures. Price \$3.50. Springfield, Illinois: Charles C. Thomas, Publisher, 1950.

This welcome monograph of the American Lecture Series is most timely. It is unique in that it integrates our rapidly developing concepts of the mechanism of asthma, based upon the complicated abnormal physiological responses and disturbed emotional personalities which comprise the physical and psychic components of the individual. With this broad concept the author attempts to apply proper physiological management when considering all of the activating forces and their evaluation. He stresses the importance of the immediate non-specific therapeutic measures for the patient acutely ill with asthma, and only then is the management of the underlying allergy undertaken. The therapeutic measures suggested are based principally on personal observations in the management by the author of over 500 patients with asthma. His therapy was based on extensive laboratory studies with a large variety of protecting drugs. In order to restore physiologic balance in the patient very ill with asthma, it was found necessary to use a large variety of properly balanced therapeutic measures.

There are ten chapters, with a bibliography and an index. These chapters include detailed reports on the use of protecting drugs, methods of sedation, supportive therapy, bronchiolar relaxation, bronchiolar evacuation or catharsis, therapeutic use of gases, and the management of infection and preventive measures.

In spite of the detailed physiologic and chemical studies, the book is very practical; and if its instructions are followed out, more relief to the patient severely ill with asthma will be obtained.

This book is printed on good paper stock, the figures are all clear, and the print is unusually large and readable. With its excellent binding and compact size, it is both a handy desk reference and a book to be slipped into the pocket.

METHODS IN MEDICAL RESEARCH, VOLUMES I AND II. Vol. I, V. R. Potter, Editor-in-Chief; 372 pages, with numerous figures. Price \$8.00. Vol. II, J. H. Comroe, Jr., Editor-in-Chief; 361 pages, with numerous figures. Price \$6.50. Chicago: Yearbook Publishers, Inc.

Review of Volume I was withheld until Volume II appeared. The governing board is composed of such outstanding scientists as Irvine H. Page, A. C. Ivy, Colin M. MacLeod, Eugene A. Stead, David L. Thomson, Henry Welch, and H. D. Green. Contributors and reviewers were selected as associate editors for their qualifications in their particular fields in medical research. Both volumes are devoted to methods and techniques. The governing board, when compiling material to make such a series useful, reasoned that there should be "appraisal and discussion of the various methods that have been proposed for the solution of some experimental problem." They realize also that it is becoming more difficult, especially in physiology, to have papers published describing techniques combined with the results obtained. In addition, these volumes provide an opportunity to publish modified techniques which frequently do not appear in print; and, lastly, they disseminate information about the various procedures developed during the war which have appeared only in official reports.

The first volume is divided into four chief self-containing sections, each representing one of the broad fields of medical research: biochemistry, physiology and pharmacology, microbiology and immunology, and biophysics including radiobiology. Step by

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step methods are described, accompanied by photographs of apparatus, tables, and graphs.

The second volume is divided into three sections: Section I deals with the methods of study of bacterial viruses; Section II is on pulmonary function tests; Section III, assay of hormone secretions. Section II should be of interest to all allergists.

Both volumes are indispensable to the scientist performing laboratory techniques. These volumes with their detailed techniques are prepared more for the experienced laboratory investigator than the medical student, unless he is doing graduate work. The books are durably bound to withstand laboratory wear. Unfortunately, the volumes are of different length and width, but this is of minor importance.

CLINICA MEDICA, Lectures on Pathology and Treatment. By Nino Marsiaj, M.D. 471 pages, 39 figures, 25 pesos (Argentine money, about \$4.00 American money). Mr. Bartolome Chiesino—El Ateneo, Florida 340-344, Buenos Aires, Argentina.

Introduction by Prof. Nicolas Romano. The author is a professor on the faculty of medicine, of the University of Porto Alegre (Rio Grande del Sud, Brasil). This book is a compilation of lectures on pathology and the clinical aspects of diseases commonly met in this section of South America, such as toxic allergy, Loeffler's syndromes, tropical eosinophilia, lambliasis, amebiasis, myasthenia gravis, etc. The illustrations are very clear. There is a reference bibliography following each chapter. It is to be regretted that there is no English translation of this book.

THE FUNDAMENTALS OF ELECTROCARDIOGRAPHIC INTERPRETATION. By J. Bailey Carter, M.D., F.A.C.P., Assistant Professor, Department of Medicine, University of Illinois College of Medicine; Attending Staff, Cook County Hospital, Augustana Hospital, Chicago. 406 pages. Price \$6.50. Springfield: Charles C. Thomas, 1949.

This volume is intended as an introduction to electrocardiography for the general physician. It is not merely a report of research, as it presents only tested facts and the consensus of workers in the field. The material is so practical that careful study of the work will enable any physician to interpret the simpler records without difficulty. Almost all hospitals are now equipped with apparatus for electrocardiographic study.

The book recognizes the importance of serial curves in the diagnosis and management of coronary disease, especially in differentiating myocardial infarction from acute coronary failure, anginal attacks, or from acute abdominal disease and other conditions which it simulates.

Each chapter begins with an authoritative discussion, followed by a number of illustrative electrocardiograms. Some of the subjects covered are the physiological basis of electrocardiography, the technique, individual wave changes, paroxysmal tachycardia, coronary occlusion, and graphic findings in a long list of various specific diseases. At the back of the book are case histories and a glossary. An up-to-date bibliography follows each chapter.

ANNALS of ALLERGY

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STANDARDIZATION OF DUST EXTRACTS

I. Standardization on the Basis of Equal Molecular Size

M. SCHERAGO, BERNARD BERKOWITZ, and MORTON REITMAN

Lexington, Kentucky

HERE is need for a certification service for allergenic extracts, comparable to certification of biological stains, that will assure the allergist of the potency and efficacy of the extracts which he purchases and uses for diagnostic and therapeutic purposes. Certification, however, is possible only if a reliable and dependable method of standardizing (or assaying) allergenic extracts is available. The methods that have been in use have been largely chemical, and they have not proven to be dependable or universally acceptable.

Recently, Rockwell, Thomas and Wittich (1947) introduced a method of standardizing house dust extracts which, on the basis of their claims, appeared to offer a satisfactory criterion for certifying such extracts. It seemed worth while, therefore, to investigate the possibility of applying their method to the certification of house dust extracts. Samples of dust extracts prepared according to their directions were, therefore, subjected to analysis and standardization by their method.

EXPERIMENTAL

Preparation of House Dust Extracts.—The samples of house dust used in this investigation were obtained from the vacuum sweepers from local theaters and hotels. A total of four individual batches of dust were obtained from three different sources. Batch 1 was obtained from the vacuum sweeper bag from a local theatre, following a routine rug sweeping. Batches 2, 3, and 4 were obtained from two local hotels which were requested to save the sweepings not only from the rugs but also from the furniture, mattresses, and drapes. In the preparation of both the crude

From Department of Bacteriology, University of Kentucky.
Presented at the Sixth Annual Meeting of The American College of Allergists, January 15-18,
1950, St. Louis, Missouri.

Dr. Scherago is an Associate Member of the American College of Allergists.

TABLE I. RESULTS OF CHEMICAL ANALYSES OF DUST EXTRACTS

Extract	Mg. total N, per ml.	Mg. P.T.A.N.* per ml.	Mg. F.A.A.N.** per ml.
M.R.	0.31450***	0.14225	0.0151
B.B.	1.20510	0.64015	0.1207
M.S.	1.31010	0.59050	0.1372
J.H.	0.67720	0.18760	0.0807
M.H.	1.50080	0.46760	0.0720
R.W.	0.99110	0.19810	0.07466

*Phosphotungstic acid precipitable nitrogen.

**Free alpha amino nitrogen determinations were made on the phosphotungstic precipitate fractions.

***Each value is the average of the results of triplicate determinations.

concentrated and the absorbed concentrated extracts from these batches of dust, the method reported by Rockwell et al was employed.

The crude concentrated extracts were labelled M.R. (from batch 1), B.B. (from batch 2), M.S. (from batch 3), and M.H. (from batch 4). The absorbed concentrated extracts were labelled J.H. (prepared from M.S.) and R.W. (prepared from M.H.).

Following their preparation, all the dust extracts were filtered through Seitz filters and the filtrates were tested for sterility. Upon confirmation of sterility a portion of each extract was removed and saved for chemical analysis. To the remainder of the extract a volume of sterile glycerin was added to make a 50 per cent solution. All the extracts were stored in sterile rubber-stoppered, heavy pyrex 250 ml. Erlenmeyer flasks at 8° C.

Chemical Standardization.—The procedures used for assaying the potency of the dust extract samples were those used by Rockwell et al (1947). Accordingly, total nitrogen, phosphotungstic acid precipitable nitrogen, and free alpha amino nitrogen determinations were made. The micro Kjeldahl procedure used for the total nitrogen and phosphotungstic acid precipitable nitrogen determinations was that of Parnas and Wagner (1931). The free alpha amino nitrogen determinations were made according to the method of Peters and Van Slyke (1932).

For all three determinations (total nitrogen, phosphotungstic acid precipitable nitrogen, and free alpha amino nitrogen) each sample was run in triplicate, and at the start of each series of runs a blank determination was made on the reagents alone.

Table I shows the results of the chemical examinations of each extract. Each value represents the average of the results of the triplicate analyses.

Standardization of the House Dust Extracts by Intradermal Testing.—

1. Comparison of skin reactions of dust extracts not diluted to a constant P.T.A. nitrogen concentration:

Each of the six extracts was dispensed, aseptically, in 10 ml. amounts, in diaphragm-stoppered vials. A set of vials was sent to each of five co-operating allergists for skin testing. The extracts were accompanied by record sheets upon which the results were to be recorded, together with other data requested (Fig. 1) and a copy of instructions.

STANDARDIZATION OF DUST EXTRACTS—SCHERAGO ET AL

Test done by Dr.	Clinical notations:			Return to Dr. M. Scherago Dept. of Bact. Univ. of Ky. Lexington, Ky.
Patient:	Dilutions	1:1000	1:10,000	1:10,000
Extract No.				
Amount Injec- ted				
Date				
Extract No.				
Amount Injec- ted				
Date				
Extract No.				
Amount Injec- ted				
Date				

Fig. 1. Sample record sheet for recording skin test reactions produced by dust extracts that had not been diluted to a constant P.T.A. nitrogen content.

INSTRUCTION SHEET

1. All tests are to be made intradermally.
2. Please keep antigens in refrigerator when not being used.
3. Use properly cleaned and sterilized sharp 26-gauge hypodermic needles and tuberculin syringes.
4. The amount injected should be 0.02 c.c., accurately measured for all tests and recorded on the data sheet.
5. The dilutions to be used are prepared with physiological saline (0.85 per cent NaCl). For dust-sensitive patients make 1:10, 1:100, 1:1,000, 1:10,000 dilutions of each sample. For non-sensitive controls use only the 1:10, and 1:100 dilutions.
6. Each patient is to be tested with all six samples in the above dilutions.
7. If possible, test at least three known dust-sensitive patients with the samples in all dilutions and one non-sensitive patient as a control.
8. Injections: Make injections approximately two inches apart with the least possible trauma in the volar surface of the forearm and lateral surface of the arm. Injections are preferably made by the same individual so that the technique will be about the same.
9. Reactions: Skin reactions may be read with a 75 watt Mazda lamp or by daylight. Observations of the skin reactions should be made at fifteen minutes and readings taken about twenty minutes after the injection. When the wheals and flares are of their maximum size they should be recorded by *one* of two methods:
 - (a) Tracings: The wheals and flares are outlined on the skin with a washable ink. Thin tissue paper is placed over them and both the wheal formation area and erythema are traced in pencil. These tracings should then be transferred by means of carbon paper to the enclosed data sheet.
 - (b) Measurements: The wheal and flare should be measured in millimeters and recorded as wheel
flare, for example a wheal measuring 1 by 1 mm. with a flare of 2 by 4 mm. should be recorded as $\frac{1 \times 1}{2 \times 4}$. A notation of "ps" should be made if pseudopodia develop; thus if there were pseudopodia it would be recorded as $\frac{1 \times 1}{2 \times 4}$ ps.

STANDARDIZATION OF DUST EXTRACTS—SCHERAGO ET AL.

TABLE II. SKIN REACTIONS TO HOUSE DUST EXTRACTS NOT DILUTED TO THE SAME P.T.A. NITROGEN CONTENT

Allergist:		Kaplan		Rockwell		Stier				Mothersill				
Patient:		A.D.	F.G.	R.	H.S.	M.H.	D.M.	F.B.	P.Mc.	S.T.	R.W.	A.B.	R.M.	M.E.
Dust Extract	Dilution													
M.R.	1-10	9x5**	0x0	13x12	15x12	8x8	10x8	12x12	7x7	10x8	9x9	*	10x10	10x12
		19x13	0x0	31x32	30x30	25x30	15x15	20x23	15x15	20x15	20x40	30x0	30x30	
	1-100	3x1	0x0	12x9	12x10	7x7	6x6	12x10	6x6	10x12	5x5	6x6	7x8	5x5
		7x6	0x0	30x30	30x25	20x20	15x15	30x30	15x15	20x22	0x0	15x16	0x0	20x50
	1-1000	0x0	0x0	5x5	9x7	6x6	0x0	10x8	6x6	0x0	10x15	7x8	0x0	5x5
		0x0	0x0	21x26	30x20	15x15	0x0	20x20	10x10	0x0	25x20	20x30	0x0	20x20
	1-10000	0x0	0x0	4x1	6x6	5x5	0x0	7x8	5x5	0x0	2x3	3x2	*	5x5
		0x0	0x0	21x21	20x20	10x10	0x0	20x15	10x10	0x0	0x0	10x5	0x0	
	B.B.	4x3	5x1	17x11	15x20	10x10	8x8	9x10	15x10	12x10	10x10	*	10x12	0x0
		16x19	26x18	42x40	30x30	25x25	10x5	30x20	25x25	35x35	20x30	0x0	0x0	
		3x3	9x6	13x10	12x12	8x8	8x8	8x9	10x12	12x14	5x5	10x8	10x10	
		12x9	26x18	30x33	25x25	20x20	15x15	20x20	20x20	25x26	15x10	20x20	20x20	20x30
	1-1000	0x0	6x1	9x10	10x8	6x6	8x8	8x8	10x12	10x10	10x10	10x12	0x0	0x0
		0x0	0x0	21x22	25x20	15x15	15x15	20x15	20x20	12x10	20x20	30x35	0x0	0x0
	1-10000	0x0	6x3	3x1	8x6	6x6	8x8	6x6	7x6	0x0	7x2	5x5	*	0x0
		0x0	0x0	14x12	20x20	10x10	15x15	20x15	15x15	0x0	0x0	25x20	0x0	
M.S.	1-10	3x3	0x0	18x16	14x12	8x8	8x8	8x8	10x12	20x10	10x10	*	12x13	15x10
		9x9	0x0	38x37	40x30	20x20	15x15	25x20	25x25	25x32	20x30	20x30	20x30	20x30
	1-100	0x0	0x0	10x14	12x10	8x6	8x8	8x8	8x6	20x18	5x5	15x10	2x3	5x5
		0x0	0x0	22x22	30x30	15x15	15x15	20x20	15x15	25x20	20x30	22x25	0x0	10x20
	1-1000	0x0	0x0	8x8	8x10	0x0	8x8	6x8	6x6	5x5	10x10	10x10	0x0	0x0
		0x0	0x0	10x12	25x30	0x0	15x15	15x15	10x10	10x10	15x15	0x0	0x0	0x0
	1-10000	0x0	0x0	4x5	8x8	0x0	0x0	5x5	6x5	10x10	10x5	3x3	*	0x0
		0x0	0x0	8x9	25x30	0x0	0x0	10x10	10x10	12x12	0x0	15x10	0x0	

*Not tested in that dilution.

**Numerator—diameters of the wheal in millimeters as measured through its two extremes.

Denominator—diameters of the flare in millimeters as measured through its two extremes.

Of the five allergists who had indicated a willingness to co-operate and to whom a set of the extracts to be tested had been sent, four responded with reports. These four allergists tested a total of thirteen house-dust-sensitive patients and six non-house-dust-sensitive controls. No positive reactions were obtained with any of the extracts in the control persons tested. The skin reactions obtained in the dust-sensitive persons are recorded in Table II. They are recorded as the diameters of the wheal in millimeters as measured through its two extremes over the diameters of the flare as measured through its two extremes. As may be seen from this table, there was considerable variation in degree of sensitivity to the six extracts among the patients tested. Nevertheless, the less reactive patients did not react at all to the extracts that produced reactions only in low dilutions in those patients that were more sensitive.

STANDARDIZATION OF DUST EXTRACTS-SCHERAGO ET AL.

TABLE II. SKIN REACTIONS TO HOUSE DUST EXTRACTS NOT DILUTED
TO THE SAME P.T.A. NITROGEN CONTENT—CONTINUED

*Not tested in that dilution.

*Numerator—diameter of the wheat in millimeters as measured through its two extremes.
Denominator—diameter of the flake in millimeters as measured through its two extremes.

In an effort to evaluate the potencies of the extracts, an evaluation code, consisting of two groups of digits, was employed. The first group, consisting of a single digit on the left, was used to indicate the highest dilution giving a reaction of at least 5 mm. by 5 mm. in size.

1 equals 1-10
2 equals 1-100

3 equals 1-1000
4 equals 1-10000

The second group, consisting of the remaining digits, was used to indicate the measurements of the wheal in millimeters in that dilution. The results of the skin reactions according to this code are recorded in Table III.

The results as recorded in this table were then averaged for each of the six extracts in the following way. The first digits representing the highest

STANDARDIZATION OF DUST EXTRACTS—SCHERAGO ET AL

TABLE III. SKIN REACTIVITY RATINGS OF DUST EXTRACTS TESTED ON DUST SENSITIVE PATIENTS

Allergist	Patient	Dust Extracts					
		Crude			Adsorbed		
		M.R.	B.B.	M.S.	M.H.	J.H.	R.W.
Kaplan	A.D.	1-9x5*	1-4x3	1-4x9	1-5x6	1-3x3	neg.
	F.G.	neg.	3-6x4	neg.	4-9x5	1-6x3	1-5x4
Rockwell	R.	3-5x5	3-9x10	3-Sx8	3-Sx7	2-9x5	neg.
Stier	H.S.	4-8x6	4-8x6	4-8x8	4-8x8	4-6x8	4-6x6
	M.H.	4-5x5	4-6x6	2-Sx6	4-8x8	neg.	neg.
	D.M.	2-6x6	4-8x8	3-Sx8	2-Sx8	neg.	neg.
	F.B.	4-7x8	4-6x6	4-5x5	4-6x6	4-6x6	4-8x8
Mothersill	P.Me.	4-5x5	4-7x6	4-6x5	4-6x6	4-5x5	4-6x6
	S.T.	2-10x12	3-10x10	4-10x10	4-7x7	2-5x5	2-6x5
	R.W.	3-10x15	3-10x10	4-10x5	3-9x9	2-5x3	neg.
	A.B.	3-7x8	4-5x5	3-10x10	3-10x12	4-5x5	4-5x5
	R.M.	2-7x8	2-10x8	1-12x13	1-10x13	1-8x7	neg.
	M.E.	4-5x5	2-10x10	2-5x5	2-10x12	neg.	1-6x7

*First digit designates the highest dilution giving a reaction 5 mm x 5 mm (1 = 1-10, 2 = 1-100, 3 = 1-1000) the second factor (e.g. 9x5) designates the diameters of the wheal in mm in that dilution.

TABLE IV. COMPARISON OF AVERAGE VALUES OF THE SKIN TEST RATINGS OF THE DUST EXTRACTS WITH THE AVERAGE VALUES OF THE TOTAL NITROGEN AND P.T.A. NITROGEN

Extract	Skin Test Rating	Total N. mg./ml.	P.T.A.N.* mg./ml.
B.B.	3.22	1.2054	0.64015
M.H.	3.16	1.5008	0.4676
M.R.	2.84	0.3145	0.1432
M.S.	2.76	1.3104	0.5905
J.H.	1.67	0.6772	0.1876
R.W.	1.57	0.9940	0.1981

*Phosphotungstic acid precipitable nitrogen.

dilution of extract that gave a positive reaction were averaged to the third decimal. Next the average diameter of the wheal was computed for each extract as tested on each patient, and these figures averaged. The resulting figure for each extract was then added to the last two digits (the second and third decimals) of the figure obtained by averaging the dilutions. In this manner the size of the reaction produced as well as the dilution of the reaction was given consideration. These average values (skin test ratings) are recorded in Table IV. As may be seen from this table, the six extracts, as tested in thirteen different house-dust-sensitive patients, ranged in potency in the following descending order, B.B., M.H., M.R., M.S., J.H., and R.W.

A comparison of the skin reactivity ratings with the results of the chemical analyses of these extracts is also shown in Table IV, and in graphic form in Figure 2. From Table IV and Figure 2, it may be seen that the skin reactivity of each of the six extracts was not a function of either the total nitrogen concentration or the phosphotungstic acid precipitable nitrogen concentration.

2. Comparison of the skin reactivities of dust extracts of approximately the same molecular size and diluted to the same P.T.A. nitrogen concentration:

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Rockwell et al (1947) reasoned that since the milligrams per ml. of P.T.A. nitrogen represent the total amount of protein nitrogen present in a sample of house dust extract and the milligrams of free alpha amino

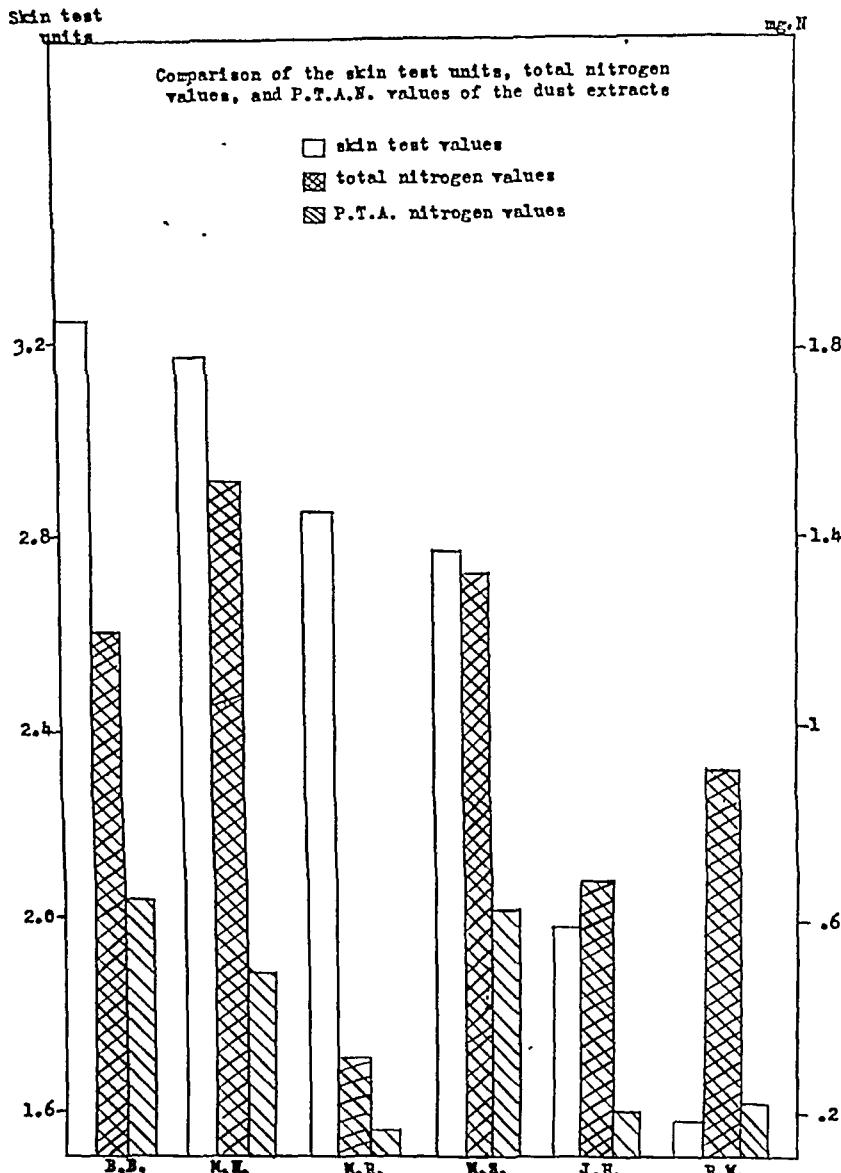


Fig. 2

nitrogen represent the number of free alpha amino groups in the total protein, it is possible to calculate, by dividing the P.T.A. nitrogen by the free alpha amino nitrogen, the average number of nitrogen atoms per molecule of sample. This, they reasoned, was possible since each protein molecule contains only one free alpha amino group. Accordingly, they calculated these values for each of the extracts that they had used. They

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then selected extracts which they considered to be of approximately the same molecular size (those that contained from 9 to 14 nitrogen atoms per molecule, or a maximum difference from the smallest to the largest of

Test done by Dr.	Clinical Notations:	Return to Dr. H. Scherago Dept. of Bact. Univ. of Ky. Lexington, Ky.
Patient:	Dilutions	
	Concentrated	1/10
Extract No.		
Amount Injected		
Date		
Extract No.		
Amount Injected		
Date		
Extract No.		
Amount Injected		
Date		

Fig. 3. Sample record sheet for recording skin test reactions produced by dust extracts that had been diluted to a constant P.T.A. nitrogen content.

TABLE V. AVERAGE NUMBER OF NITROGEN ATOMS PER MOLECULE OF THE PREPARED EXTRACTS

	Extract	Average Number of Nitrogen Atoms per Molecule
Crude	M.R.	3
	B.B.	5
Adsorbed	M.S.	4
	M.H.	6
Adsorbed	J.H.	2
	R.W.	3

5 atoms). They diluted each of these extracts so as to contain 0.300 mg. of P.T.A. nitrogen per ml. From these diluted extracts they prepared 1-100 and 1-1000 dilutions and mailed them to co-operating allergists with instructions to test the dilutions in both sensitive and nonsensitive persons.

When we calculated the average number of nitrogen atoms per molecule of extract of our extracts, using the values recorded in Table I, we obtained the results recorded in Table V. The figures recorded in this table are the whole numbers most closely approximating the decimal values obtained by dividing the P.T.A. nitrogen by the free alpha amino nitrogen values. Only whole numbers were used because fractions of a nitrogen atom cannot exist. Each of the extracts was diluted to contain 0.003 mg. of P.T.A. nitrogen per ml., which is the amount that was contained in the 1-100 dilution of Rockwell et al. Each extract that was so diluted was dis-

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TABLE VI. SKIN REACTIONS TO HOUSE DUST EXTRACTS DILUTED
TO THE SAME P.T.A. NITROGEN CONTENT

Numerator—diameter of the wheal in millimeters as measured through its two extremes.
Denominator—diameter of the flare in millimeters as measured through its two extremes.

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TABLE VII. SKIN REACTIVITY RATINGS OF DUST EXTRACTS AFTER DILUTION TO A CONSTANT CONCENTRATION OF P.T.A. NITROGEN

Allergist	Patient	Extracts					
		Crude			Adsorbed		
		M.R.	B.B.	M.S.	M.H.	J.H.	R.W.
Brown	A.F.	3-13x10*	3-8x6	3-12x6	3-9x7	3-8x5	3-8x4
	R.A.	3-13x9	3-8x10	3-10x8	3-6x10	3-9x12	3-10x8
	P.N.	3-13x9	3-11x9	3-10x7	3-8x8	3-7x10	3-10x8
	S.G.	3-9x8	3-8x5	3-7x6	3-6x6	3-7x3	2-6x6
	E.M.	3-10x10	3-8x8	3-11x12	3-7x7	3-6x5	3-8x5
	V.M.	3-17x12	3-8x6	3-7x6	3-7x5	3-5x5	3-6x7
	S.A.	3-9x9	3-8x8	3-8x6	3-10x13	3-7x6	3-5x8
	H.W.	3-16x12	3-16x15	3-8x6	3-8x7	3-8x6	3-12x9
Hyman	W.R.	3-6x8	3-10x8	3-6x6	3-9x6	3-7x7	3-7x5
	P.L.	3-13x10	3-14x12	3-9x7	3-14x10	3-13x10	3-8x10
	E.S.	3-12x8	3-7x4	3-5x5	3-6x5	3-4x6	3-8x5
	S.	3-13x9	3-8x6	3-11x9	3-10x10	3-8x8	2-8x5
Davison	P.C.	3-5x7	2-5x4	0x0	2-3x3	0x0	0x0
	M.H.	2-10x10	2-12x10	2-7x6	2-9x10	0x0	2-8x6
	L.H.	2-5x5	2-5x5	2-4x6	2-5x5	0x0	0x0
	M.M.	2-5x5	2-2x2	0x0	2-4x4	2-5x5	0x0

*First digit designates the highest dilution giving a reaction 5 mm by 5 mm (2 = undiluted; 3 = 1-10). The second factor (e.g. 12x10) designates the diameters of the wheal in millimeters in that dilution.

pensed in diaphragm-stoppered vials and appropriately labelled. A set of samples of all the extracts was mailed to each of five allergists for intradermal testing. Accompanying the extracts were record sheets (Fig. 3) upon which the results were to be recorded and a list of directions identical with those given in the preceding experiments, except for item 5 which was changed to read as follows: "The dilutions to be injected are (1) concentrated, (2) 1-10 dilution of the concentrated prepared with physiological saline (0.85 per cent NaCl)." Thus each allergist was instructed to use the same dilutions employed by Rockwell et al.

Of the five allergists to whom samples were sent for skin testing three responded with reports. The three allergists tested a total of sixteen patients that were sensitive to dust and an additional five patients that were not sensitive. In every case the six extracts failed to produce a reaction when tested in the non-dust-sensitive controls. The results of the skin reactions as tested in the dust-sensitive patients are recorded in Table VI. Here too, the skin reactions are recorded as the diameters of the wheal in mm. measured through its two extremes over the diameters of the flare in mm. measured through its two extremes. The results of the skin tests were condensed and evaluated according to the code given above for that purpose. In accordance with the practice of Rockwell et al, only the size of the wheal was considered in evaluating the potency of the extracts. The values thus obtained are recorded in Table VII. As may be seen from Table VII, there is considerable variation in the degree of sensitivity among the patients. Thus eight patients tested by Dr. Brown seemed to be highly reactive to our samples, in contrast to the four patients tested by Dr. Davison. The four patients tested by Dr. Hyman seemed to be moderately reactive. Despite the variations in the degree of sensitivity between the individual patients the trend establishing the relative order of potency of the six ex-

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tracts was consistent. For example, extract M.R. was the most reactive in eleven cases and second most reactive in three additional cases of the sixteen patients that were tested.

TABLE VIII. AVERAGE VALUES OF THE SKIN TEST RATINGS OF THE DUST EXTRACTS AFTER DILUTION TO A CONSTANT P.T.A.N.*
CONCENTRATION

	Dust Extract	Average Rating of Skin Tests
Crude	M.R.	2.92
	M.H.	2.83
	B.B.	2.80
Ad-sorbed	M.S.	2.56
	J.H.	2.46
	R.W.	2.25

*Phosphotungstic acid precipitable nitrogen

The averages of the skin test values, computed in the same way as those in the previous experiment, were then determined for the six extracts. These averages arranged in the order of potency of the extracts are recorded in Table VIII. As may be seen from this table, extracts M.R., M.H., and B.B. (with molecular sizes of 3, 6, and 5, respectively) gave approximately the same skin test ratings. M.S. and J.H. (with molecular sizes of 4 and 2, respectively) also differed very little from each other in their skin test ratings. There was, however, no correlation between the skin test ratings of M.S. and J.H. and those of M.R., M.H., and B.B. and none between the skin test rating of R.W. (molecular size of 3) and that of any of the other extracts. For the six extracts the skin reactivity varied from a value of 2.25 to one of 2.92. A comparison between the averages of the skin test values, as shown in Table VIII and the concentrations of phosphotungstic acid precipitable nitrogen is shown graphically in Figure 4. As may be seen from this figure, while the phosphotungstic acid precipitable nitrogen of the extracts remained constant at 0.003 mg./ml., the skin reactivity varied considerably. These wide variations in potency are in contrast to the findings of Rockwell et al who reported approximately equal skin reactions to the extracts which they had standardized in this manner.

DISCUSSION

In our attempt to apply the method of standardizing dust extracts proposed by Rockwell, Thomas and Wittich (1947) to the certification of such extracts, every effort was made to follow as explicitly as possible the directions which they gave not only for analyzing and standardizing the extracts but for their preparation as well. Prior to the performance of the chemical analyses on the six house dust extracts, numerous preliminary trials were performed on carefully prepared and standardized solutions in order to become as expert as possible in the techniques involved. Standard

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solutions of urea were prepared and analyzed by the micro Kjeldahl procedure. These preliminary analyses were carried out until the correct values of nitrogen were consistently obtained. Repeated determinations of

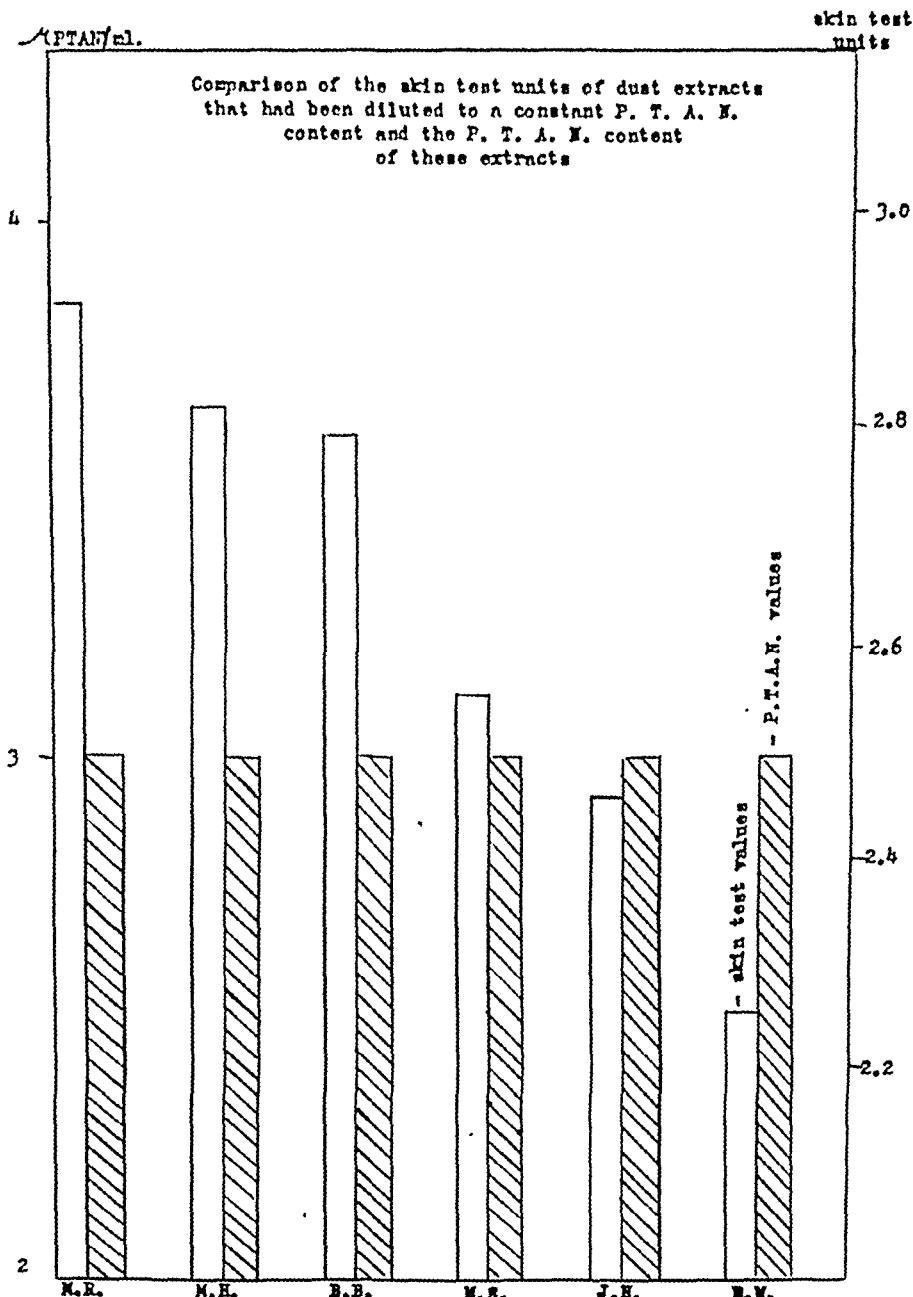


Fig. 4

free alpha amino nitrogen were carried out on prepared samples of glycine by the Van Slyke procedure under the instruction and guidance of a trained and experienced operator of this apparatus until consistently accurate results were obtained. All the tests were carried out by two workers working together and checking each other.

Our failure to obtain any correlation whatsoever between the skin test

activities of the six dust extracts which we prepared and examined and their total or phosphotungstic acid precipitable nitrogen content confirms the findings in this respect of Rockwell et al and of others and substantiates the observations of many workers, including Arbesman and Eagle (1939) and Sutherland (1945), who believe that estimations of nitrogen are not valid criteria for determining allergenic potencies.

When our extracts, which were all of approximately equal molecular size, were each diluted to contain 0.003 mg. per ml. of P.T.A. nitrogen and tested on both sensitive and non-sensitive persons, as was done by Rockwell et al, considerable variation was found in the skin potencies of the extracts. This finding was in marked contrast to that of Rockwell and his colleagues, who found almost perfect agreement in the potencies of the extracts which they studied in this manner.

Because of our failure to confirm the latter finding of Rockwell et al, the data in their report were subjected to a very thorough analysis in the hope that we might find some explanation for the disagreement between their results and ours. This analysis revealed certain discrepancies in their data. According to Table V of their report, extracts AA, RB, UF, WX, MB, and MC, all of approximately equal molecular size, gave, after dilution to a constant protein nitrogen concentration and after injection in only 1-100 and 1-1000 dilutions, skin reactivity ratings above 3.50 in every case, except one, in which the rating was 3.47. From the evaluation key on page 31 of their report the maximum reaction obtainable with a 1-1000 dilution was 3. It was difficult, therefore, to understand how they could have arrived at skin reactivity ratings averaging above 3. Furthermore, in Table IV, these same extracts, with the exception of MC, which were tested before they were diluted to a constant phosphotungstic acid precipitable nitrogen concentration, show no correlation between their skin reactivity ratings and their phosphotungstic acid precipitable nitrogen content. For example, extract WX, which contained 0.3238 mg. of phosphotungstic acid precipitable nitrogen per ml., gave a skin reactivity rating of 5.00, while extract UF, which contained 0.9680 mg. of phosphotungstic acid precipitable nitrogen per ml., gave a skin reactivity rating of only 3.90. It was difficult to understand how two extracts of approximately equal molecular size, one containing three times the phosphotungstic acid precipitable nitrogen concentration as the other, and having a skin reactivity rating of 3.90 as compared to a rating of 5.00 for the other, could produce, after dilution to equal phosphotungstic acid precipitable concentrations, skin reactions of the same magnitude. These discrepancies were, therefore, called to Dr. Rockwell's attention and Dr. Rockwell concurred in our criticism. Dr. Rockwell agreed that there appeared to be some error in the published paper. After he had had an opportunity to compare the published paper with the original manuscript, he wrote that in reference to the skin reactivity ratings of the molarly standardized extracts all averaging above 3.00, the code used to arrive at these values in the

original manuscript was erroneously omitted by the editors of the journal in which the paper was published. The code that was omitted from the published paper was as follows:

Dilution	Average Diameter of Wheal in Millimeters	Rating of Skin Reactivity
1-1000	10 or more	5
	8 or 9	4
	5, 6, or 7	3
1-100	5 or more	2
	3 or 4	1

With regard to the discrepancy concerning the lack of correlation between the skin test values of the same extract when tested non-molarly and molarly, he stated that again the editors were at fault. All the extracts tested on a molar basis had been purified (no method stated) before they were analyzed chemically and tested for skin potency. The statement in the manuscript regarding the necessity for purifying these extracts before skin testing and the letter S which had been added to the designations of the extracts to distinguish the purified extracts from the crude ones from which they had been derived (e.g. W.X. to W.X.S.) were erroneously omitted from the published paper.

It is unfortunate, of course, that such serious editorial errors should have been made in the published Rockwell report. However, although the corrections listed by Dr. Rockwell would seem to explain satisfactorily the discrepancies in the report, they do not account for our failure to confirm the findings in that report. When we found that the code for evaluating skin reactivity, as published in the report, was not sensitive enough to detect all the variations in our molarly standardized extracts, we adopted an alternative procedure. It was the results of the evaluation of our extracts by this procedure that failed to confirm the findings of Rockwell et al. After Dr. Rockwell revealed that a more sensitive code had been used by him and his colleagues, we applied this code to our data. The results which we obtained on the basis of this code are given in Table IX. As may be seen from this table, even by the use of this code the marked degree of variation between the molarly standardized extracts is clearly revealed.

Since it has not been proved that the active fraction in dust extracts is a protein, it would appear to be unsound to base any chemical assay procedures upon the estimation of nitrogen in any form. However, even assuming that the house dust active component is a protein, it is possible that the amounts of this active protein component in various dust extracts may vary considerably while the total protein content, as estimated by P.T.A. nitrogen, remains constant. It appears obvious, therefore, that a chemical method of standardization that is based upon the estimation of an unknown entity is not well founded.

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TABLE IX. SKIN REACTIVITY RATINGS OF PREPARED EXTRACTS
DILUTED TO A CONSTANT P.T.A. NITROGEN CONCENTRATION*

Allergist	Patient	Extract					
		Crude			Adsorbed		
		M.R.	B.B.	M.S.	M.H.	J.H.	R.W.
Brown	A.F.	5	3	5	4	3	3
	R.A.	5	4	5	4	5	4
	P.N.	5	5	4	4	4	4
	S.G.	4	3	3	3	3	2
	V.M.	5	3	3	3	3	3
	E.M.	5	4	5	3	3	3
	S.A.	4	3	3	5	3	3
	H.W.	5	5	3	3	3	5
Hyman	W.R.	3	4	3	3	3	3
	P.L.	5	5	4	5	5	4
	E.S.	5	3	3	3	3	3
	S.	5	3	5	5	4	2
Davison	P.C.	3	1	0	1	0	0
	M.H.	2	2	2	2	0	2
	L.H.	2	2	1	2	2	0
	M.M.	2	1	0	1	2	0
Average values		4.06	3.19	3.13	3.19	2.75	2.56

*These ratings were derived according to the evaluation code which Dr. Rockwell et al used, as stated in a letter from him April 25, 1949, but which was omitted in error from the original manuscript. This code is given in detail on page 450.

The certification of allergenic extracts based on methods of standardizing that require the use of human volunteers for skin testing or passive transfer tests present certain practical difficulties. They require the co-operation of many allergists and numerous volunteers. Considering the number of allergenic extracts used by allergists it would appear impossible to enlist the large army of allergists and volunteers that would be required. In this investigation, for example, in which only six extracts were studied, letters were sent to eighteen prominent members of the American College of Allergists in an effort to enlist their co-operation in this project. Of this number fifteen replied that they would be able to help, but with varying degrees of reservation, and three indicated that they had no available time. Dr. F. W. Wittich, Secretary of the American College of Allergists, was asked to include in one of his newsletters a request for volunteers to help in this project. Replies were received from fourteen allergists. Of the group of fifteen prominent members of the American College of Allergists, samples were mailed to ten. Of these ten allergists, six responded with reports, one stated that he had lost his protocol, and three failed to reply. Of the fourteen allergists who responded to the newsletter request, extracts were mailed to one, and reports were received from him. Of the total of seven allergists who sent in reports, only one allergist responded in less than a month after we had mailed the extracts, four allergists in from one to three months, and two allergists in three months or more. This is not intended as a criticism of the allergists who offered to help in this project but serves rather as evidence that the co-operation of overworked allergists could not be expected in a certification program based upon skin testing of human beings.

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SUMMARY AND CONCLUSIONS

Six house dust extracts were prepared, analyzed for total nitrogen and for phosphotungstic acid nitrogen by the methods of Rockwell, Thomas and Wittich, and tested for skin potency by the intradermal injection of persons sensitive to house dust. In confirmation of their findings and of those of others, no correlation was found between the skin potencies of the extracts and their total nitrogen or P.T.A. nitrogen content.

The six extracts were found to be approximately equal in molecular size. When they were diluted to the same phosphotungstic acid nitrogen content and tested for skin potency by the intradermal injection of persons sensitive to house dust they failed to elicit skin reactions of the same magnitude. This finding is in contrast to the findings of Rockwell et al.

Since the active substance responsible for the allergenic potency of dust extracts is not known, methods of standardization that are based on determinations of nitrogen in any form cannot be depended upon to yield reliable information concerning the allergenic potency of these extracts.

The certification of allergenic extracts on the basis of a method of standardizing that requires the use of human volunteers for skin testing is not feasible.

ACKNOWLEDGMENTS

The authors are indebted to Dr. Ethan Allan Brown, Dr. Hal Davison, Dr. Charles Hyman, Dr. Morris Kaplan, Dr. M. H. Mothersill, Dr. George E. Rockwell, and Dr. Robert Stier for performing the skin tests. They are also indebted to Dr. Rockwell for his valuable counsel and criticism.

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ANNIVERSARY OF MEDICAL JOURNAL

The ANNALS OF ALLERGY acknowledges receiving a copy of the Spring Issue of the Hebrew Medical Journal, *HAROFE HAIVRI*, Volume I, 1950, of their 23rd anniversary year. This volume contains various subjects of interest to our readers. The Journal, edited by Moses Einhorn, M.D., is written in Hebrew with English summaries. In the current number a symposium is presented on various phases of disease and health in Israel. Among the articles of interest are "Orthopedic Problems in Israel" by I. Pulvermacher, M.D.; "Fighting Deafness in Israel" by Ahron Schwarzbart, M.D.; and "The Labor Health Service in Israel" by Moshe Rabinowitz of Tel Aviv.

STANDARDIZATION OF DUST EXTRACTS

II. In Vitro Leukocytolysis in the Assay of the Allergenicity of Dust Extracts

BERNARD BERKOWITZ AND M. SCHERAGO
Lexington, Kentucky

HERE is general agreement among allergists that methods of standardizing allergenic extracts on a biological basis are to be preferred to any chemical method. Unfortunately, the only biological methods that are acceptable today are those which involve the skin testing of human beings known to be sensitive to the allergens to be standardized. These methods do not lend themselves readily to the testing of large numbers of allergenic extracts, as would be required in a certification program. An attempt has, therefore, been made to develop a method of standardizing allergenic extracts by the use of animals instead of human beings.

In developing the method, some reaction was sought that was common to both allergy in human beings and anaphylaxis in animals. It was hoped that if some quantitative relationship could be found to exist between such a reaction in human beings and in animals, it could possibly be used to standardize allergenic extracts.

The findings of Squire and Lee (1947) appeared to point to such a possibility. These authors reported that heparinized blood from a ragweed-sensitive patient when incubated with ragweed antigen caused lysis of the white cells approximately in proportion to the degree of sensitivity of the patient. It was reasoned, therefore, that the degree of lysis might be also proportional to the concentration of active principle in the antigen. Katz (1940) had shown that heparinized blood from sensitized rabbits, upon incubation with homologous antigen, caused a marked increase in the amount of plasma histamine, while blood from non-sensitive rabbits and plasma from sensitive rabbits failed to show such an increase; and, since Code (1937) had showed that the major portion of the blood histamine is contained in the leukocytes, it was reasoned that the histamine released in Katz's work may have been from leukocytes that had undergone lysis. If it could be proved that the leukocytolytic reactions that occur in rabbits are analogous to those that occur in human beings it was felt that rabbit cell leukocytolysis might be used as a means of standardizing allergenic extracts.

EXPERIMENTAL

Preliminary Experiment Using Blood from Rabbits Sensitized with Egg Albumin.—A preliminary experiment was run in an attempt to demonstrate this phenomenon of leukocyte destruction, using egg albumin as an-

Department of Bacteriology, University of Kentucky.

Presented at the Sixth Annual Meeting of the American College of Allergists, January 15-18, 1950, St. Louis, Missouri.

Dr. Scherago is an Associate Member of the American College of Allergists.

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TABLE I. PERCENTAGES OF DECREASE IN THE NUMBER OF LEUKOCYTES NOTED AFTER INCUBATING EGG ALBUMIN SENSITIVE RABBIT'S BLOOD WITH DILUTIONS OF EGG ALBUMIN

Concentration of Egg Albumin in Blood from Sensitized Rabbit	Number of Leukocytes	Percentage of Decrease in the Leukocytes
1-10	2800	58.8
1-100	4016	40.9
1-1000	4950	27.2
1-10000	5850	14.0
saline	6800	
1-200	2050	61.6
1-400	2250	58
1-800	2800	47.6
1-1600	3550	33.6
1-3200	3900	27.1
saline	5350	
1-2000	4000	23.8
1-4000	4650	11.4
1-8000	4800	8.6
1-16000	5200	1.0
1-32000	5300	0
saline	5250	

tigen and the heparinized blood from rabbits sensitized with this antigen.

A rabbit was injected intravenously with 1 ml. of 10 per cent solution of egg albumin every third day until a total of 4 ml. had been injected. Twenty-one days after the last injection, 9 ml. of blood were drawn from the marginal ear vein into a calibrated centrifuge tube containing 1 ml. of a stock heparin solution (25 mg. of heparin in 10 ml. of 0.85 per cent saline solution). The tube was stoppered and inverted several times to mix. Forty-five hundredths milliliter amounts of heparinized blood were then added to chemically clean serological tubes containing 0.05 ml. amounts of varying dilutions of egg albumin in saline, and to one tube containing 0.05 ml. of physiological saline solution. These tubes were then stoppered with corks, gently inverted six times, and placed in a water bath at 37° C. for sixty minutes. The tubes were then removed from the water bath and again inverted gently six times. White cell counts were made from the diluted blood in each tube in the usual way. The experiment was performed three times using concentrations of 1-10, 1-100, 1-1000, and 1-10,000 of the egg albumin in the blood the first time, 1-200, 1-400, 1-800, 1-1600, and 1-3200 the second time, and 1-2000, 1-4000, 1-8000, 1-16000, and 1-32000 the third time.

As a control, blood from two normal rabbits that had not been previously injected with egg albumin was examined in the same manner as above with the exception that the 1-2000, 1-4000, 1-8000, 1-16000, and 1-32000 dilutions of egg albumin were not used. The percentage of decrease of these controls was found to be less than 5 per cent.

The results of this preliminary experiment with the blood from the sensitized rabbit are given in Table I. As may be seen from this table, the blood from the rabbit that was sensitized to the egg albumin showed leukocytolysis, upon *in vitro* incubation with egg albumin, in approximate proportion to the concentration of the antigen. The trend indicated in each of the three attempts is not a constant one; that is, there is no consistent

quantitative relationship between the concentration of egg albumin and the percentage of decrease in the number of leukocytes. The consistent failure of the blood from normal rabbits to show this marked decrease in the number of leukocytes indicates that this phenomenon is the result of a specific antigen antibody reaction.

*Experiments with Rabbits Injected with House Dust Extracts.**—Ten rabbits were injected with house dust extracts in the following manner:

Rabbit 5M was injected with house dust extract B.B. which had been preserved with 50 per cent glycerin. One milliliter of this extract was injected intravenously every third day until a total volume of 4 ml. had been given. Rabbits 6 and 8M were injected with house dust extract M.R. which had been preserved with 50 per cent glycerin. One milliliter of this extract was injected intravenously into each rabbit every third day until 4 ml. had been given.

Rabbits 9 and 10 were injected with house dust extract M.S. which had been preserved with 50 per cent glycerin. One milliliter of this extract was injected intravenously into each rabbit every third day until a total of 4 ml. had been given.

Rabbits 5R, 8R, 7, and 11 were injected intracutaneously once a week for thirteen weeks with 0.5 ml. amounts of a mixture consisting of one part of house dust extract and 1 part of staphylococcus toxin. The staphylococcus toxin was obtained from a sterile broth filtrate of a forty-eight-hour culture of *Micrococcus pyogenes* var. *aureus*, obtained from the stock culture collection of the Department of Bacteriology at the University of Kentucky. It was shown by Burky (1934) that it is possible to render rabbits sensitive to ragweed antigen by either injecting the filtrate of a "*Staphylococcus aureus*" culture that had been grown in a broth containing ragweed extract, or by injecting toxin in one site and ragweed extract in another. In our work the toxin was given with the dust extract in a mixture of equal parts of toxin and house dust extract M.R.

Rabbit 14 was injected with an emulsion of house dust extract, oil, and heat-killed *Mycobacterium tuberculosis*. This emulsion was prepared according to the method of Freund and McDermott (1942). Aquaphor and heavy paraffin oil were sterilized in the autoclave. The bacterial culture was autoclaved at 15 pounds for fifteen minutes. The growth was removed from the surface of the coagulated egg medium and the organism dried *in vacuo* and weighed. Ten milliliters of dust extract M.S. plus 10 ml. of the sterile aquaphor were blended in a sterile Waring Blender, and 20 ml. of the sterile paraffin oil, containing 40 mg. of the dried *Mycobacterium tuberculosis* var. *hominis*, strain H. 37 R.V., were added and blended. The resulting antigen was aseptically transferred to sterile vials. Fifteen-tenths milliliter amounts were injected intraperitoneally into each rabbit once weekly for eleven weeks.

*For a description of these extracts see the paper by Scherago, Berkowitz, and Reitman (1950).

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TABLE II. RESULT OF LEUKOCYTOLYSIS EXPERIMENT WITH RABBIT "SHOCK BLOOD" AND SERIAL DILUTIONS OF BOTH HOMOLOGOUS AND HETEROLOGOUS DUST EXTRACTS

Blood from Rabbit Number	Sensitized to Dust Extract	Tested with Dust Extract	Leukocyte Count and Per Cent Decrease in Number of Leukocytes with Dust Extract Diluted						Saline Control
			1-10	1-20	1-40	1-80	1-160	1-320	
6	M.R. glyc.	M.S.	*	5900 45	5750 46.5	6550 39.1	7550 29.8	7850 27	10750
6	M.R. glyc.	M.R.	*	3150 53.3	4100 39.2	4750 29.7	4350 35.6	4800 28.9	6750
6	M.R. glyc.	M.R.	2050 46.6	3050 20.8	2900 24.7	3100 19.5	2700 30	*	3850
6	M.R. glyc.	M.R.	*	5550 32	5200 36.2	7500 8	5700 30	6800 16.5	8150
8R	M.R. S.t.	M.R.	*	4550 46.5	5700 33	6050 28.8	6600 22.3	6650 21.8	8500
8R	M.R. S.t.	M.R.	*	5700 46.3	6950 34.5	7350 30.6	9250 12.7	9250 12.7	10600
8R	M.R. S.t.	M.R.	*	6300 37.6	7350 27.2	7550 25.2	6500 35.6	7200 28.7	10100
8R	M.R. S.t.	M.R.	*	5450 46	5050 50	7850 22.3	6600 34.6	7750 23.1	10100
8M	M.R. glyc.	M.R.	6150 38	6850 31.8	9450 5.3	9450 5.3	9250 7	8950 10	9950
8R	M.R. S.t.	B.B.	5000 54.7	5450 50.7	8250 25.4	7300 33.9	12100 0	*	11050
5M	B.B. glyc.	B.B.	8350 14.7	7050 28	9000 8.1	9850 0	10600 0	*	9800
10	M.S. glyc.	M.S.	*	5800 25.6	8000 0	7350 5.8	7450 4.5	7500 3.8	7800
9	M.S. glyc.	M.S.	*	8150 41	11550 16.3	12500 9.4	10850 21.4	11750 14.9	13800
N-1	none	M.R.	5600 .89	5550 1.8	4600 18	5050 0	5350 5.3	5650 0	5650
N-2	none	M.R.	*	9900 6.6	10400 1.8	12000 0	11250 0	10200 3.8	10600
N-3	none	M.R.	*	9650 1.7	10100 0	9300 5.1	10200 0	9450 3.6	9800

Glyc. = injected with glycerine.

S.t. = injected with *Staphylococcus* toxin.

*Not tested with that dilution.

In from four days to one week after the last injection 10 ml. samples of blood were obtained aseptically from each rabbit by cardiac puncture. The sera were separated from the clots and transferred aseptically to sterile test tubes for later use (see Experiments 3, 4, and 5b). Enough crystalline merthiolate was added to each tube of serum to make a final concentration of 1-1000.

1. Leukocytolysis, experiments using serial dilutions of house dust extracts and blood from house dust sensitive rabbits:

Rabbits 5M, 6, 8R, 9, and 10 were utilized in this experiment. Twenty-one days after the last injection of dust extract, each rabbit was bled from the marginal ear vein into a calibrated centrifuge tube containing 0.5 ml. of the stock heparin solution until 5.5 ml. of blood were obtained. Forty-five-hundredths milliliter amounts of a sample of blood were added to

tubes containing 0.05 ml. amounts of a 1-2, 1-4, 1-8, 1-16, and 1-32 dilution of one of the following dust extracts: M.R., B.B., or M.S., and to a control tube containing 0.05 ml. of physiological saline solution. Each tube was stoppered with clean corks, inverted gently six times, and placed in a water bath at 37° C. for sixty minutes. After this period of incubation the tubes were removed from the water bath and again inverted gently six times, after which samples were withdrawn from each tube into leukocyte diluting pipettes for counting. After the counts were made in the usual manner, the percentages of decrease in the blood-dust extract mixtures as compared with the blood-saline controls were determined. Samples of blood from three rabbits (N_1 , N_2 , and N_3) that had not been previously injected with dust extract were used as controls and tested in the same manner as the blood from sensitive rabbits.

The results of the leukocyte counts, accompanied by the percentages of decrease obtained, are shown in Table II. As may be seen from this table, no significant decrease resulted with any of the dilutions tested when blood from noninjected (control) animals (N_1 , N_2 , and N_3) was used. Of thirteen trials with the blood from the dust-injected rabbits the highest percentage of decrease in the number of leukocytes was obtained with the lowest dilution of dust extract in nine trials, and the least percentage of decrease in the number of leukocytes was obtained with the highest dilution of dust in seven trials. In these experiments the trend showing leukocytolysis in approximate proportion to the concentration of antigen is not of a quantitative nature. Nevertheless, the decrease that occurred corresponds roughly to the concentration of antigen.

2. Leukocytolysis experiments using 1-2 dilutions of house dust extracts and blood from rabbits sensitized to dust:

Since the degree of leukocytolysis in the animals injected with house dust extracts corresponded roughly to the concentration of dust extract with which the blood of these animals was tested, this experiment was conducted in an attempt to see if these shock bloods would reveal differences in potency among the extracts tested. Rabbits 6, 8M, and 9 were used in this experiment. Forty-five-hundredths milliliter amounts of heparinized blood from each rabbit were added to tubes containing 0.05 ml. amounts of a 1-2 dilution of the six house dust extracts and to a control tube containing 0.05 ml. of saline solution. The tubes were then inverted, incubated, and inverted again; and the leukocytes were counted as in the previous experiment, except that counts were made in both counting chambers instead of in only one, and the number of cells in the two chambers was averaged. This precaution was taken in the hope of obtaining more consistent results. In Experiment 1 it was shown that a particular dilution of extract in a given trial gave a greater percentage of decrease than a more concentrated dilution. By counting more cells it was felt that this error might be minimized.

The results of the leukocyte counts, together with the corresponding

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TABLE III. RESULTS OF LEUKOCYTOLYSIS EXPERIMENT WITH WHOLE RABBIT "SHOCK BLOOD" AND DUST EXTRACTS

Blood from Rabbit	Leukocyte Count and Per Cent Decrease in Number of Leukocytes with Dust Extract						Saline Control
	M.R.	B.B.	M.S.	J.H.	M.H.	R.W.	
SM 28.5	6100 28.5	6150 31.3	7600 15.3	9150 0	6950 22.4	8200 8.4	8950
	6750 14	6200 21	7000 10.8	7850 0	6950 11.5	7100 9.5	7850
SM 13.2	6600 13.2	6300 17	6800 10.5	7700 0	*	*	7600
	7250 18.1	6900 22	6450 27	7850 11.3	6100 31	7150 19.2	8850
6 31.6	6300 31.6	6700 27.2	6900 25	9100 1.1	6450 29.9	7550 17.9	9200
	6450 13.5	5600 24.8	5950 20.1	5750 22.8	6400 14.2	6150 17.4	7450
6 31.6	5300 31.6	5300 31.6	5850 21.6	6550 15.5	7350 5.1	6900 10.9	7750
	5650 42	5500 43.5	6200 36.5	6750 30.8	6550 32.9	7450 23.6	9750
9 31.2	6950 31.2	5900 41.5	6500 35.6	6900 31.6	6000 40.5	7200 28.7	10100
	6250 27.3	6850 20.4	5900 31.4	7100 17.3	6900 19.8	7650 11	8600
Average percentage of decrease	25.1	28	23.7	13.1	23	16.3	
Average deviation from the mean	±2.6	±2.2	±2.3	±3.3	±2.8	±1.6	

*Not tested with that extract.

percentages of decrease obtained in this experiment, are recorded in Table III. The percentages of decrease for each extract from ten trials were averaged and the errors of these average values were calculated. As may be seen from this table the average values of the percentages of decrease descend in magnitude in the following order: B.B. 28, M.R. 25.1, M.S. 23.7, M.H. 23, R.W. 16.3, and J.H. 13.1 per cent. If the extracts are arranged in order of potency on the basis of the skin test values* obtained with them the following sequence is obtained: B.B. 3.22, M.H. 3.16, M.R. 2.84, M.S. 2.76, J.H. 1.97, and R.W. 1.57. The skin test potencies and the average leukocytolysis values of the extracts are shown graphically in Figure 1. As may be seen from this graph, extracts B.B., M.R., M.S., and J.H. show the same relative potencies when tested by both of these methods.

3. The demonstration of specific leukocytolysis using *in vitro* sensitized rabbits' blood:

The results of Experiment 2 indicated considerable variation in the percentage of decrease evoked by a single extract from one trial to another. This error was dramatized by determining the reliability of the average values obtained as represented by the average deviation of the mean for each dust extract. The average deviation of the mean values are recorded

*See Table IV in the first paper of this series by Scherago, Berkowitz, and Reitman. Ann. Allergy, 8:437-452, 1950.

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in Table III. As an example of this variation, extract M.R. has an average percentage decrease value, determined by averaging ten trials, of 25.1 per cent. The individual values in the ten trials ranged from a low of 13.2

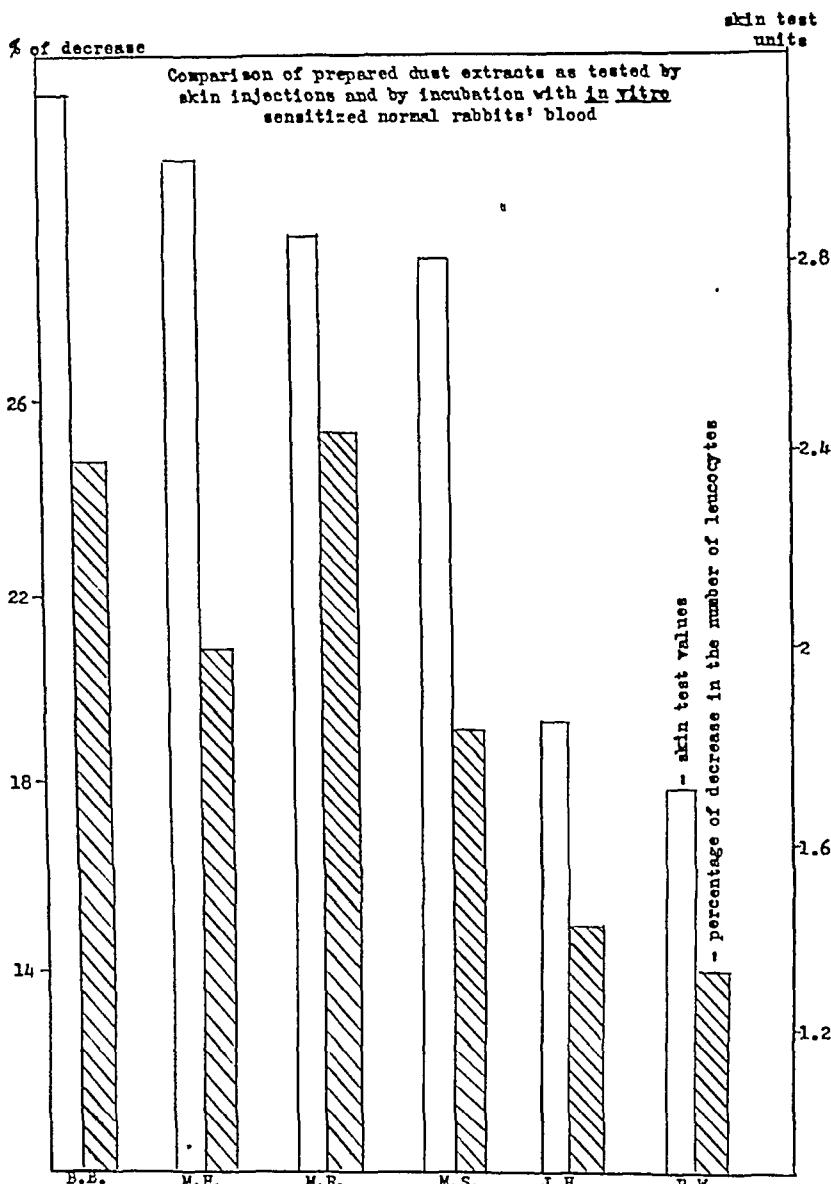


Fig. 1

per cent to a high of 42 per cent. A possible explanation for this error was thought to be the different degrees of sensitization of the particular animal for that day and the number of leukocytes present in that particular animal for that day. To remedy this partially an attempt was made to sensitize, *in vitro*, leukocytes from a normal rabbit by incubating this rabbit's whole blood with dilutions of an antiserum against house dust extract that had

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**TABLE IV. PERCENTAGES OF DECREASE IN THE NUMBER OF LEUKOCYTES
OBTAINED USING *IN VITRO* SENSITIZED NORMAL RABBITS' BLOOD
PREPARED WITH DIFFERENT DILUTIONS
OF RABBIT HOUSE DUST ANTISERA**

Anti-serum*	Dust Extract Used for Testing	Leukocyte Count and Per Cent Decrease in Number of Leukocytes in Antisera Dilution					Saline Control
		1-10	1-20	1-40	1-80	1-160	
SR	M.R. glyc.**	4150 30.8	3950 34.2	2850 52.5	3700 38.4	5450 9.2	6000
SR	M.R. glyc.	5400 37.7	4600 46.8	4000 53.8	4800 44.5	7900 8.7	8650
SR	M.R. glyc.	5300 0	4900 0	3950 20.2	4650 6	4800 3	4950
SR	M.R. glyc.	5000 24.2	4350 34.1	4150 37.2	4450 32.6	4500 31.8	6000
SR	B.B. glyc.	5750 12.9	5500 16.7	4650 29.8	5100 18.2	6000 9.1	6000
SR	M.R. glyc.	4350 17.9	3650 30.8	3550 33	4050 23.6	4050 23.6	5300
5R	M.R. glyc.	4700 28.8	3900 41	3500 47	4850 26.5	5750 12.9	6000
8R	M.R. glyc.	5400 17.5	4850 26	5100 22.2	5050 22.9	5750 12.2	6550

*The antiserum designation is derived from the animal supplying the serum.

**Glyc. =preserved with glycerine.

been prepared in another rabbit. Blood was obtained from normal rabbits in the usual manner and heparinized. Forty-five-hundredths milliliter amounts were added to serological tubes containing 0.05 ml. of undiluted, and 1-2, 1-4, 1-8, and 1-16 dilutions of dust extract antisera from rabbits 8R, 5R, and 8M, and to a control tube containing 0.05 ml. of saline solution. These tubes were cork-stoppered, inverted six times, incubated at 37° C. for sixty minutes, and again inverted six times, after which 0.05 ml. of house dust extract diluted 1-2 were added to each tube. The tubes were again inverted, incubated, inverted again, and counted in the usual manner. The results of eight such determinations are recorded in Table IV. From this table it can be seen that the maximum amount of leukocytolysis was obtained when a final concentration of 1-40 antiserum in blood was used. Any greater concentration of antiserum resulted in a prozone phenomenon.

4. Assay of dust extracts by means of *in vitro* sensitized blood:

Since it was found possible to sensitize passively the leukocytes of blood from normal rabbits with rabbit dust extract antisera, an attempt was made to determine the potencies of the six dust extracts by incubating them with blood thus sensitized. The sensitization for these experiments was accomplished by placing 3.6 ml. of heparinized blood in a $\frac{5}{8}$ by 5 inch test tube containing 0.4 ml. of a 1-4 dilution of rabbit dust extract antiserum. The tube was stoppered, inverted six times, and incubated at 37° C. for sixty minutes, after which it was again inverted six times. Forty-five-hundredths milliliter amounts of the sensitized blood were then transferred to serological tubes containing 0.05 ml. amounts of the six dust

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TABLE V. THE PERCENTAGES OF DECREASE IN THE NUMBER OF LEUKOCYTES OBTAINED BY INCUBATING PREPARED HOUSE DUST EXTRACTS WITH IN VITRO SENSITIZED RABBITS' BLOOD

Blood of Animal Used	Sensitizing Antiserum used (dilution 1-10)	Leukocyte Count and Per Cent Decrease in Number of Leukocytes with Dust Extract						Saline Control
		M.R.	B.B.	M.S.	J.H.	M.H.	R.W.	
N-1	8R	5950 29.6	4600 45.5	6200 26.6	6650 21.4	5500 34.3	6600 21.9	8450
N-2	5R	5750 19.6	5150 28	6650 7	6500 9.1	6300 11.9	6200 13.3	7150
N-2	5R	3700 32.8	3900 29.1	3900 29.1	5100 7.3	3750 31.8	4050 26.2	5500
N-1	5R	6550 20.6	5600 31.5	6600 20	6500 21.4	6850 17	7200 12.7	8250
N-2	5R	5900 19.7	5450 25.9	6750 8.1	6700 8.8	6900 6.1	6500 11.5	7350
N-1	5R	6100 33.7	6450 30	6250 32	7200 21.8	6650 27.8	7750 15.8	9200
N-3	5R	6300 24.7	6400 22.9	6850 17.5	7700 7.1	6750 18.7	7650 8	8300
N-2	5R	6900 19.7	7250 15.7	7000 18.3	7250 15.7	7550 12.6	7850 9.1	8600
N-1	5R	3750 46.9	3750 46.9	4450 36.9	5500 21.9	4750 32.6	5650 19.8	7050
N-2	5R	6850 22.6	7450 15.8	7100 19.8	8300 6.2	7150 19.2	7400 16.4	8850
N-3	8R	4900 17.7	5100 9.2	4800 19.3	4800 19.3	5150 13.4	4900 17.7	5950
N-1	5R	6950 27.3	7000 26.7	8250 13.6	8250 13.6	8100 15.2	8700 8.9	9550
N-2	5R	6350 35	6400 34.4	6550 32.6	6850 29	6700 31.2	7650 21.5	9750
N-3	5R	5100 25.6	4700 31.4	6050 11.3	6250 8.7	5050 26.3	5800 15.5	6850
N-1	5R	6700 8.2	6850 6.1	6350 13	7250 .7	5850 19.2	7300 0	7300
N-2	5R	6750 14.6	7100 10.1	7150 9.5	6650 15.8	6950 12	7100 10.1	7900
N-3	5R	4450 23.3	4000 31	4800 17.3	4850 16.4	4600 20.7	5200 10.7	5800
N-1	8R	4600 30.3	5100 22.8	5150 22	5300 19.7	5000 24.2	5450 17.5	6000
N-2	8R	4900 31.4	5300 25.9	5950 16.8	6300 11.9	5300 25.9	6200 13.3	7150
N-3	8R	4400 30.1	5300 15.9	5450 18.5	5300 15.9	4900 22.2	5650 10.3	6300
Average percentage of decrease		25.6	25.2	19.2	14.1	21.1	14.0	
Average deviation from the mean		±1.5	±1.8	±1.4	±1.3	±1.5	±1	

extracts, and to one tube containing 0.05 ml. of saline solution. These tubes were then inverted, incubated at 37° C. for sixty minutes, and then reinverted, as was done in the preceding experiment. Leukocyte counts were then made from the contents of each tube. The entire procedure as outlined was repeated twenty times. The results of these twenty trials and the percentages of decrease in the number of leukocytes are recorded in Table V. The average percentages of decrease for each dust extract and

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the errors of these average values were calculated and are also given in Table V. As may be seen from this table, the average percentages of decrease show considerable improvement in reliability as compared to the

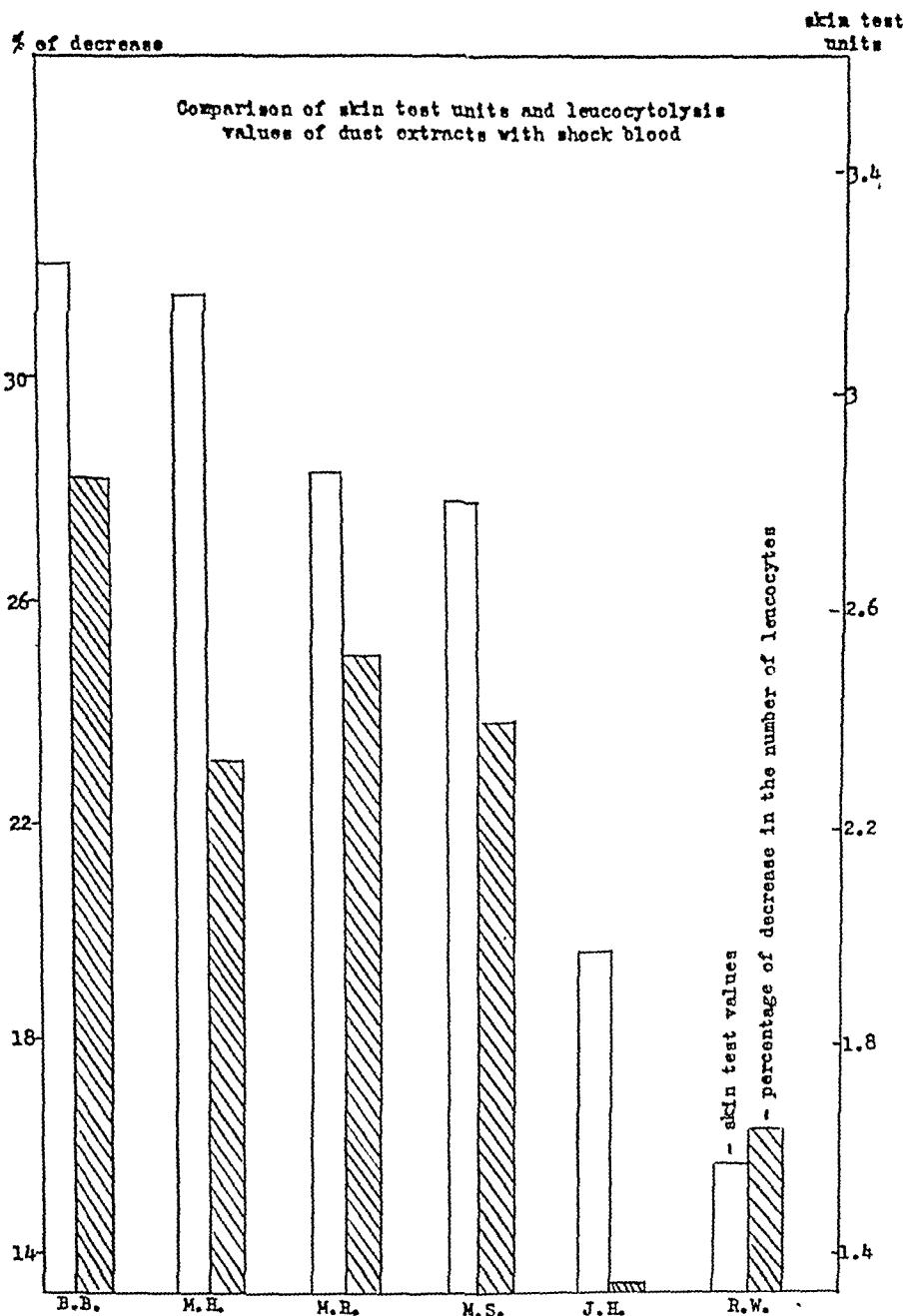


Fig. 2

results obtained using whole shock blood from anaphylactically sensitive rabbits. The maximum error recorded in this experiment is 1.8 as compared to a maximum error of 2.8 recorded in the experiment using whole shock blood. The average values obtained by using *in vitro* sensitized cells show the extracts to range in potency as follows: M.R. 25.6, B.B. 25.2, M.H. 21.1, M.S. 19.2, J.H. 14.1, and R.W. 14. These average values of

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TABLE VI. PERCENTAGES OF DECREASE IN THE NUMBER OF LEUKOCYTES OBTAINED USING COMMERCIAL DUST EXTRACTS AND BLOOD FROM SENSITIZED RABBITS

Animal Used	Leukocyte Count and Per Cent Decrease in Number of Leukocytes with Dust Extract							Saline Control
	9200	CAC-1	CAC-2	CAC-3	CAC-4	19916	1A50-B	
9	6800 23.2	8950 0	7300 17.5	8000 9.6	8850 0	3750 35	8200 7.2	8850
9	7150 15.3	8000 9.6	8250 6.8	7750 12.1	8400 5.1	6000 32.2	8050 9.1	8850
9	8200 16.8	8850 10.2	9000 8.7	9050 8.1	9550 3	6250 36.6	8150 17.3	9850
9	7850 22.6	9900 2.5	9250 8.8	9250 8.8	10750 0	7050 30.5	7450 26.6	10150
9	7600 21.2	8250 14.5	7000 27.5	8350 13.5	7950 17.6	5600 42	7550 22.8	9650
9	7350 6.1	8350 0	10650 0	7300 7	8150 0	5900 25	7000 10.8	7850
9	10350 10	8800 23.2	10250 10.3	10550 8.3	9950 13.1	7200 37	9300 18.8	11450
7	6250 12	6100 9.9	6900 2.8	6450 9.1	6950 2.1	4450 37.1	6400 9.9	7100
11	7450 20.8	9050 3.7	8950 4.8	8100 13.8	9050 3.7	5750 38.8	7500 20.2	9400
14	5600 26	6350 15.9	6500 13.9	6400 15.2	6800 9.9	4150 11	5900 21.8	7550
9	7050 23.4	8850 3.8	8150 11.1	7500 18.5	8500 7.6	5850 36.4	8150 11.4	9200
7	6450 18.9	7550 5	7200 9.4	7100 10.7	7400 6.9	4700 40.9	7450 6.3	7950
9	18650 8.8	19900 2.7	20350 4	19100 6.6	18050 11.7	14400 29.6	16650 18.5	20450
Average values	17.3	7.8	9.4	10.9	6.2	35.5	15.3	

percentage of decrease for each extract are plotted in graph form in Figure 2 together with the skin test values for each extract. As may be seen from this graph, the six extracts with the exception of extract M.R. show the same relative potencies when tested by both of these methods.

5. Assay of commercial house dust extracts by *in vitro* leukocytolysis.

An attempt was made to apply the *in vitro* leukocytolysis principle to the assay of commercial house dust extracts. For this purpose seven commercial extracts were obtained from four manufacturers as indicated below.

Samples C.A.C.-1, C.A.C.-2, C.A.C.-3, and C.A.C.-4 were obtained from Company CAC. These samples were labeled "preservative 50 per cent glycerin."

Sample 9200 was obtained from Company CCY. This sample was labeled "preserved with 0.4 per cent tricresol."

Sample 1A50-B was obtained from Company LD. This sample had no indicated preservative.

Sample 19916 was obtained from Company PC. This sample was labeled "0.5 per cent in 50 per cent glycerin."

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TABLE VII. THE PERCENTAGES OF DECREASE IN THE NUMBER OF LEUKOCYTES OBTAINED USING COMMERCIAL DUST EXTRACTS AND IN VITRO SENSITIZED RABBITS' BLOOD

Blood of Rabbit Used	Sensitizing Antiserum Used (Dilution 1-10)	Leukocyte Count and Per Cent Decrease in Number of Leukocytes with Dust Extract							Saline Control
		9200	CAC-1	CAC-2	CAC-3	CAC-4	19916	1A50-B	
N-1	5R	4200 28.2	5150 6.8	6100 0	6350 0	5150 12	3650 37.6	5150 12	5850
N-2	5R	5150 18.2	7050 0	6100 0	6150 2.3	5450 13.5	5050 19.8	4850 23	6300
N-1	5R	6000 21	8200 0	8050 0	7950 0	7450 2	5950 21.8	6350 16.5	7600
N-2	5R	6850 20.8	9950 0	7950 8.1	8500 1.7	7600 12.1	4500 48	6850 20.8	8650
N-1	5R	5450 23.8	6200 13.3	6700 6.4	6150 9.8	6900 3.5	4800 32.8	6900 3.5	7150
N-1	5R	5850 12.7	6850 0	6800 0	6600 1.5	6350 5.2	4850 27.6	6400 4.5	6700
Average values		20.8	3.3	2.4	2.5	8.1	31.1	13.3	

(a) Assay with whole blood from sensitized rabbits: The seven extracts were tested by adding 0.45 ml. amounts of heparinized shock blood to serological tubes containing 0.05 ml. amounts of the samples. These tubes were incubated and counts were made as in the preceding experiments. The results of thirteen trials are recorded in Table VI. As may be seen from this table, the seven extracts, on the basis of percentage decrease of leukocytes, range in potency as follows: 19916 35.5, 9200 18., 1A50-B 15.3, CAC-3 10.9, CAC-2 9.4, CAC-1 7.8, CAC-4 6.2. For control purposes, the seven extracts were tested with the blood of normal rabbits which had not been previously injected with house dust. In no case was there any leukocyte destruction greater than 5 per cent in these controls.

(b) Assay with *in vitro* sensitized blood from normal rabbits: Heparinized blood from normal rabbits was sensitized *in vitro* with dust extract rabbit antiserum in the same manner as in Experiment 4. The sensitized blood was incubated with the commercial dust extracts and counts were made as was done in Experiment a. The results of the leukocyte counts accompanied by the percentages of decrease observed for the seven extracts as tested in six different trials, are recorded in Table VII.

As may be seen from this table, the seven extracts on the basis of percentage decrease of leukocytes range in potency as follows: 19916 31.1, 9200 20.4, 1A50-B 13, CAC-4 8.1, CAC-1 3.3, CAC-3 2.5, CAC-2 2.3

Thus, by both methods of assay extracts 19916, 9200, 1A50-B ranged in potency in that order. The CAC extracts by both methods were the least potent. However, the four extracts from this company did not react in the same order by both methods. By the first method they ranged in the following order CAC-3, CAC-2, CAC-1, CAC-4; and by the second, CAC-4, CAC-1, CAC-3, and CAC-2.

DISCUSSION

The *in vitro* bio-assay procedure for determining the allergenic potencies of house dust extracts that was developed in this investigation was based on the following considerations. Histamine is a mediating substance in both anaphylaxis in animals and allergy in human beings. Katz (1940) had demonstrated that whole blood from sensitive rabbits released enough histamine upon *in vitro* shock to play a significant role in anaphylaxis, and Squire and Lee (1947) had showed that leukocytolysis occurred when heparinized blood from ragweed sensitive patients was incubated with ragweed pollen extracts. It was hoped, therefore, that a quantitative relationship might be found to exist between the degree of leukocytolysis of cells from dust-sensitized rabbits and the concentration of the active fraction in the dust extracts being tested, comparable to the quantitative relationship that exists between human skin sensitivity and the concentration of this fraction.

Later in the investigation, advantage was taken of the report of the success of Dragstedt, Arellano, Lawton, and Youmans (1940) in passively sensitizing, *in vitro*, the blood of normal rabbits, to modify the procedure by substituting for the blood of sensitized rabbits blood from normal rabbits that was passively sensitized, *in vitro*, with the serum from immunized rabbits.

Before applying the leukocytolysis bio-assay procedure to the standardization of dust extracts a preliminary experiment was conducted with egg albumin, an antigen of proven potency, in order to test the method and to become proficient in the technique. The results of this experiment revealed that although the percentages of decrease in the number of leukocytes were not absolutely in proportion to the concentrations of the antigen, in general, the greatest amount of leukocytolysis occurred when the higher concentrations of antigen were used and the least amount of leukocytolysis when the lower concentrations were used. These results appeared to be sufficiently encouraging to warrant the testing of the method with house dust extracts.

The first experiment with house dust extract, which was essentially a repetition of the egg albumin experiment, yielded approximately the same results as were obtained with the egg albumin. Here again, in general, the lower concentrations of dust extract caused the lower decrease in the number of leukocytes and vice versa. That the leukocytolysis observed was not due to some leukotoxic substance in the dust extract was shown by the relative absence of leukocytolysis in the control experiments in which blood from normal rabbits was substituted for the blood from the sensitized ones.

Despite the lack of absolute correlation between the percentage of decrease in the number of leukocytes and the concentration of egg albumin or dust extract, it was thought worth while to determine the relative potencies of the six dust extracts by the method of leukocytolysis and to com-

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pare them with the relative potencies of these extracts as determined by skin tests on dust-sensitive patients. When the six extracts were arranged in order of potency on the basis of leukocytolysis (Tables III and V, and Figs. 1 and 2), this arrangement was approximately, though not absolutely, comparable to the arrangement of the extracts on the basis of their skin reactivity. For example, extracts B.B., M.R., M.S., and J.H. showed the same relative potencies when they were tested by their ability to produce leukocytolysis in shock rabbits' blood as they did when they were tested by skin reactivity. This correlation between the extracts was even closer when *in vitro* passively sensitized rabbits' blood was substituted for blood from actively sensitized rabbits. Extracts B.B., M.H., M.S., J.H., and R.W. showed the same relative potencies by both methods.

In the course of the experiments with the blood from sensitized rabbits considerable variation was noted in the percentages of decrease with a particular dust extract from one experiment to another of the same type. In an effort to minimize this error, blood from normal rabbits that was passively sensitized, *in vitro*, with rabbit house dust antisera was substituted for the blood from sensitized rabbits. It was reasoned that the different rabbits used as the source of shock blood, regardless of how they were sensitized, each had a different degree of sensitivity, and this variation in sensitivity might have been responsible for the large degree of variation in our early experiments. In an effort to obtain leukocytes with a more constant degree of sensitization, blood from normal rabbits was sensitized, *in vitro*, with a constant amount of antiserum. The results obtained by this modification showed some improvement as evidenced by the decrease in the error obtained. The maximum error with blood from sensitive rabbits was plus or minus 2.8 while with the passively sensitized blood it was no more than plus or minus 1.8.

Although the *in vitro* bio-assay procedure developed in this investigation did not yield results which would point to the applicability of this method in its present stage of development to the standardization of dust extracts, it is felt that the results are sufficiently encouraging to warrant further investigation and, perhaps, modification of the method. It is felt that the principles upon which this method is based appear sounder than those of the chemical methods.

Among the modifications to be tried is the use of standard suspensions of leukocytes that have been separated from the other blood cells and have been sensitized, *in vitro*, with a standard amount of a standard antiserum. The means of determining the efficacy of this procedure might also be modified by using a serum neutralization procedure for this purpose instead of skin sensitivity tests. This would eliminate the discrepancies arising from the varying degrees of sensitivity in sensitive persons. With these modifications it is possible that the results obtained will be consistent enough to have quantitative significance.

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SUMMARY AND CONCLUSIONS

A method of standardizing dust extracts was developed based on the fact that leukocytes from the blood of sensitized animals, or leukocytes from the blood of normal rabbits that had been passively sensitized *in vitro* with serum from sensitized rabbits, are lysed when they are incubated *in vitro* with the homologous antigen. When this method was applied to the standardization of six dust extracts, it was found that on the basis of the per cent of decrease in the number of leukocytes the relative potencies of the extracts paralleled closely their relative potencies on the basis of their skin reactivities. Closer agreement was obtained when passively sensitized cells were used instead of cells from sensitized rabbits.

The leukocytolysis method, in its present state of development, cannot be used to standardize dust extracts. However, the results obtained are encouraging enough to warrant further study of this method with certain suggested modifications.

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ERUPTION FOLLOWING HOME PERMANENT

The consensus of investigators who have conducted toxicologic studies on these products [home permanent wave sets] is that when reactions occur they usually take the form of a contact dermatitis. Goldman, and others (Permanent Wave Process, *J. A. M. A.* 137:354 [May 22] 1948) stated: "Cold waving solutions are used extensively, and the frequency of reactions is reported to be less than 0.1 per cent. The reactions may be characterized either as varying degrees of primary irritation or, more rarely, as instances of eczematous hypersensitivity." The use of these products in the presence of an existing dermatitis is inadvisable. Representative manufacturers include a caution statement to this effect in their directions for use.—From Queries and Minor Notes, *J.A.M.A.*, July 22, 1950.

THE IMMUNOLOGICAL PROPERTIES OF ALCOHOL

A Survey of the Literature

MARGARET W. ROBINSON

Seattle, Washington

RECENT increased interest in the problem of chronic alcoholism and renewed investigation of the concept that there is a biological basis for the development of this disease have led to an extensive review of the literature for evidence that ethyl alcohol may have allergenic or antigenic properties. Many of these reports have never been indexed in this country; indeed, few have been cited in the English language. Thus it appears timely to review the reports which have appeared since the first serotherapeutic method for alcoholism was proposed in 1896, to evaluate so far as possible their immunological significance and to point out some of the investigations necessary to any confirmation of the antigenic or allergenic properties of ethyl alcohol.

To clarify this discussion, the following definitions have been adopted:

1. *Chronic alcoholism*: a disease characterized by continued incapacitation of the subject for normal life because of steady or periodic ingestion of alcohol. Chronic alcoholism may be primary or may be secondary to other physical or mental disorders, but in this discussion primary chronic alcoholism is the usual concern.
2. *Tolerance*: the ability of the individual to resist the *characteristic* response to alcohol. In this review, resistance to the physiological effects of alcohol is the predominant concern.
3. *Intolerance*: The existence of a very low resistance to the *characteristic* response to alcohol.*
4. *Allergy or hypersensitivity*: a specific but abnormal response of the individual to alcohol, wherein it acts as an antigen and the response is due to the toxic effects of the *in vivo* formation of a specific antigen-reagin complex.
5. *Susceptibility or abnormal reaction*: an abnormal response of the individual to alcohol, including responses that are less definite manifestations of allergy (e.g., excessive motor activity, nervousness, et cetera).
6. *Habituation*: a state of being accustomed to the regular ingestion of alcohol, irrespective of whether tolerance is increased or decreased, or whether the response is normal or altered.
7. *Need*: dependence on the ingestion of alcohol. Physiological need implies a demand for alcohol created by a specific adaptation of the body which makes the substance "valuable." Physiological need is not a corollary of tolerance (which is known to exist during periods of abstinence without involving the occurrence of disturbing reactions) but should be considered to be the expression of an abnormal reaction to alcohol. Psychological need may be considered to be the expression of an abnormal desire for the effects of alcohol irrespective of tolerance, susceptibility or physiological need.

*Supported by a grant to the Research Foundation for Alcoholism by Shadel Sanitarium, Seattle, Washington.

From the Department of Physiology and Biophysics, School of Medicine, University of Washington, and Research Foundation for Alcoholism, Seattle, Washington.

*The term "intolerance" has been used by many to denote both lack of tolerance and susceptibility. Since such dual usage leads to confusion, the reviewer has interpreted the term in accordance with the context of its use: when a direct quotation is employed, the proper connotation is indicated.

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8. *Craving:* a term used to denote both physiological and psychological need. Its use will be avoided, but where necessary the proper connotation will be indicated.

ALLERGIC REACTIONS TO ETHYL ALCOHOL

The first to suggest that abnormal reactions to and need for alcohol resulted from the development of a reagin ("antibodies," to quote the author) was Ashworth (1929-32^{6,7,8,9}). He considered periodic sprees as "explosions" resulting from an accumulation of reagin; and withdrawal symptoms, experienced in breaking alcohol addiction, as the result of dissemination of the irritating reagin throughout the body. This explanation of the occurrence of sprees was most original, but no experimental evidence was offered to support it. It is difficult to see how any accumulation of presumably unbound reagin could be responsible for the phenomenon, especially since it is implied that the accumulations occur during periods of abstinence when no antigen is available to stimulate reagin production. Similarly, Ashworth's explanation of withdrawal symptoms would be more adequate if the symptoms were the result of an antigen-reagin complex which persists for some time after its formation.

Both Silkworth (1937¹⁰) and Lee (1938¹¹) stated that alcoholism is an allergic reaction. Silkworth treated it with an "appropriate colloidal preparation such as . . . orthocolloidal iodine complex or orthocolloidal gold" to "revitalize the cells," a very nonspecific treatment. Cowles (1941¹²) likened the edema of nerve cells after administration of alcohol to the nasal turgescence found in pollen allergy and treated chronic alcoholism by repeated withdrawal of spinal fluid to lessen the edema. At first glance Seliger (1939¹³) and Shadel (1944¹⁴) may seem to hold similar views. Actually, they have drawn an analogy between the "household" term "allergic reaction" and alcoholism only as a vivid means of emphasizing the importance of abstinence to patients, but not with intent to imply that allergy to alcohol exists.

In 1947 Meerloo¹⁵ reported a death from acute intoxication which resembled anaphylaxis and summarized the evidence which has led many to speculate that the sudden susceptibility to alcohol which develops in chronic alcoholics may be similar to the development of a protein allergy.

It is still theoretical whether we are allowed to speak of a real alcoholic allergy, as we speak of some protein allergies. Indeed, we have to prove that there first is an initial sensitizing dosage and that the second reaction is quantitatively and qualitatively different from the initial one. However, in medical literature the word is used in a much wider sense. Even when we do not know how some drugs act as sensitizers and what kind of allergens are produced, the clinical facts as such exist. For example, the Herxheimer reaction after neosalvarsan intoxication is explained in this way. Barbiturates and chinin have such a sudden allergic reaction. Nirvanol in children may give the same reaction. Some students think that the drug changes the proteins of the body and that an allergic reaction develops as a reaction towards this deformed protein. Clinically it is known that several narcotic drugs develop their intolerant [abnormal—Reviewer] reactions only in combination with certain foods, meat, fish, etc. Especially with drugs applied to the skin, many allergic

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reactions are observed (resorcinum, iodoform). With some drugs this allergic factor should be related to the CH_3 group or the NH_2 group. With other drugs it is known that the allergy develops as a photogene allergy, i.e., only in combination with intense ultraviolet rays. Epstein could prove this form of photogene allergy for sulfanilamide. It is generally known that the exogenous irritant can be changed in the body into an allergen.

What do some clinical facts tell us about alcohol? Here, too, exists a form of sudden intolerance [susceptibility—Reviewer] with a complete different clinical reaction. The patients react with collapse after a relatively small quantity of alcohol. There is tremor, vomiting, dizziness, nystagmus, ataxia, tremendous hiccup. The patients have a pale face with a typical mask of roughly spread vasodilations, but there is no change in consciousness. Days afterwards they cannot bear the smell of alcohol and once they experience such a reaction, for long periods they become dizzy soon after relatively small quantities of alcohol.

Where do we meet such reactions?

We see them in chronic alcoholics.

Lemere and his associates³³ likewise stated in 1943 that "susceptibility to alcohol is often constitutional and akin to an allergy or an idiosyncrasy to a drug."

There have been two detailed descriptions of the allergic activity of ethyl alcohol. In 1938 Perlman⁴⁹ reported its occurrence in a patient who, during skin tests by the scratch method, reacted to alcoholic extracts of allergens, but did not react to nonalcoholic extracts of the same allergens when nonalcoholic antiseptics were used for skin disinfection. The patient, a middle-aged nun with a history of symptoms strongly suggestive of allergic rhinitis and asthma, stated that there were no signs of hypersensitivity to the ingestion of small quantities of alcohol during religious rites. It was considered improper to attempt a provocative test by asking her to imbibe any alcohol and, since she moved to another city, further studies could not be carried out.⁵⁰

In 1945 Haxthausen²⁷ reported a case of eczema elicited by epidermal contact with ethyl alcohol. The eczema disappeared on cessation of contact and could be subsequently elicited at will either by epidermal application of alcohol or by ingestion of alcoholic beverages. Patch tests with varying concentrations of alcohol showed the strongest reactions in the range of 10 to 20 per cent; intracutaneous injection of 1 or 2 per cent ethyl alcohol in saline gave no reaction. Four months later this patient was examined by Lomholt³⁷ and reactions were elicited only by absolute, by 91 per cent and by 60 per cent ethyl alcohol. In the interval between examinations the patient, a physician, had substituted nonalcoholic antiseptics for disinfecting her hands, and it is apparent that her sensitivity decreased with the lessened exposure. It would be interesting to know how she would react to patch tests if exposure to alcohol was increased again.

Additional impetus to the idea that an allergic reaction may be involved in the response to alcohol comes from the alcohol susceptibility skin test. Bonazzi reported in 1934¹⁴ that application of alcohol-soaked patches to the slightly scarified skin of subjects produced intense local reactions lasting

three to six hours in non-drinkers but very little reaction in habitual drinkers. In 1939 Nagle¹⁶ reported employing intracutaneous injections of ethyl alcohol to study this reaction in both nonalcoholic and alcoholic subjects. According to his report, subjects showing the strongest reaction to this test exhibited the greatest psychological impairment after the ingestion of alcohol; conversely, those showing the least reaction exhibited the least impairment, i.e., possessed the greatest tolerance to alcohol. Nagle suggested that the test could be used as a guide in the regulation of alcohol intake by patients undergoing treatment for alcoholism. After making similar observations in 1941, Kelley and Barrera²⁰ concluded that reactions to the alcohol susceptibility skin test vary inversely with tolerance to alcohol when the results of the tests are correlated with subjective and objective observation of individuals having varying concentrations of alcohol in the blood. After commenting on Silkworth's interpretation of the nature of alcoholism, they state:

Such an hypothesis of alcoholism, as an allergic condition resulting from a physiological sensitivity, would help explain individual differences in alcohol susceptibility on the basis of varying inherent sensitivity and could account to some degree, for tolerance changes and increasing susceptibility with prolonged indulgence. Furthermore, it would serve as a basis for better understanding of the mechanism of the alcoholic susceptibility test.

Although the consensus is that a strong reaction to the alcohol susceptibility skin test signifies low tolerance and a weak reaction, high tolerance, it has not been shown that there is any relationship between the degree of the reaction and the occurrence of abnormal responses to alcohol. Since Nagle stated that the pharmacological response is less (i.e., tolerance is greater) in those habituated to alcohol and that the response was the same in all subjects tested, he failed to differentiate between normal but regular drinkers and abnormal drinkers, or between abnormal drinkers who have suffered no loss of tolerance and those whose tolerance has decreased. To sustain the postulate of Kelley and Barrera that alcoholism is an allergic condition and that the alcohol susceptibility skin test supports the postulate, it should be shown that reactions to the test differentiate between normal and abnormal drinkers with equal tolerance to alcohol. Until this has been shown, or until the complete mechanism of the alcohol susceptibility skin test has been demonstrated, it does not seem proper to consider that the test provides more than an indication of variations in tolerance to alcohol.

Summary.—The two reports on systemic response to alcohol and the theoretical papers reviewed here may not warrant conclusions, but they afford some basis for the idea that an allergic reaction to alcohol may enter into the problem of the individual response to alcohol.

ANTIGENIC ACTIVITY OF ETHYL ALCOHOL

The preparation and use of antialcoholic sera, with their implication of an antigenic activity of ethyl alcohol, antedate the idea of allergic reactions

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to alcohol by many years. It was quite natural that, shortly after methods of serotherapy were developed, the possibility of their application to the scourge of alcoholism should have been considered. The basic hypothesis for this method of treating alcoholism was stated best by Sapelier and Dromard:⁵⁶ "If it is true that an antitoxic substance is developed in the blood of an animal submitted progressively to alcoholic toxins, might this substance not be utilized in another animal suffering from the same intoxication to aid it in combatting the intoxication?"[†] Although this hypothesis seemed logical at that time it needs verification and amplification for the following reasons: (1) It fails to explain why continued ingestion of alcohol does not provoke formation of sufficient antibody to make the habitual drinker immune to its effects, or why, after a period of apparent partial "immunity" to its effects, the "immunity" may suddenly disappear. (2) It fails to account for physiological need for alcohol, since known antibodies or reagins have not been shown to cause physiological dependence on an antigen. (3) It does not take into account the possibility that alcohol may be allergenic rather than antigenic. A survey of the various methods of preparing antialcoholic sera and of their use is essential for evaluating the antigenicity of alcohol.

PREPARATION OF ANTIALCOHOLIC SERA

In 1896 Toulouse^{61,65} reported the preparation of the first antialcoholic serum. He gave dogs about 40 gm. of ethyl alcohol per day for six days; fasted them the seventh day and on the eighth day bled them. No mention was made of any further treatment of the serum, or of the performance of toxicity tests before it was administered to a patient.

The blood and serum of horses which had ingested alcohol were commonly used for the treatment of alcoholism. F. M. Evelyn of San Francisco (as reported in 1899 by Caze¹⁸ and in 1900 by Regnier^{52*}) developed Equinine, blood impregnated disks of filter paper for application to the skin of alcoholics. Horses were given two to three pints of whisky per day for about three months and when microscopic examination of the blood showed the red cells to be "thick, viscous and syrupy," the horses were bled. Filter paper was then dipped in the blood and dried at high temperature.

The first report on antialcoholic horse serum was made in 1899 by Broca-Soucellier, Sapelier and Thébault,** and in 1903 its preparation was described in detail by Sapelier and Dromard.⁵⁶ Horses were given moderate, increasing doses of ethyl alcohol, twice a day, until a maximum dose of about 500 gm. was reached on the tenth day. Sapelier and Dromard specified that no animal be used which did not accept alcohol willingly, and that the animals show no ill effects or even excitation from the doses.

[†]Reviewer's translation.

*No reference can be found to Evelyn's original article. These citations both refer to an account by Caze, M.: Vaccination contre l'ivrognerie. *Hyg. usuelle*, (Jan. 14) 1899, which is not available in the United States.

**This report was published only by title in the Bull. Acad. Méd., Paris, Dec. 26, 1899, and all information comes from the book by Sapelier and Dromard.⁵⁶

These stipulations arose from their belief that the animals should approximate the human state of latent alcoholism, or "alcoholomania," for which the serum was to be employed. By the tenth day, examination of the blood usually showed that the red cells were losing the regularity of their shape, ceasing rouleaux formation, and appearing to agglutinate or be "coupled with each other;" that the white cell count was greatly increased; and that "fatty granules" (refractile granules of the eosinophiles?) were present, or were greatly increased. When this blood picture appeared, blood was drawn aseptically and the serum recovered. The serum was sealed in ampules and heated three times, at two-day intervals, for one hour at 56° C. Sapelier's criterion for the absence of toxicity in the serum was the lack of any reaction by guinea pigs to administration of 30 c.c. of serum. Whether further inoculation and bleeding of the horses was done was not stated. Sapelier and Dromard objected strongly to increasing the titer by *in vitro* treatment of the serum (Broca-Soucellier†) on the grounds that the activity of the serum must be due to antibody titer attained during exposure to alcohol if the serum was to be considered an antiserum.

In the period following the work of Sapelier and his associates, methods of preparing antialcoholic sera for therapeutic use were less well described. Blasco in 1905,¹³ Delfino in 1913²¹ and Berillon in 1919¹¹ referred to preparation of antialcoholic horse serum at the Instituto Ferran de Sagrene (Barcelona) but gave no details. Delfino did cite Ferran's claim that if the serum was kept from light and heat, it might retain 10 per cent of its activity for a year and a half. Delfino also mentioned an auxiliary product for oral reinforcement of serotherapy, called "antiethylene hemoglobin with stroma of red blood cells," which was prepared by Ferran from the blood of horses which had been accustomed to alcoholic drinks. This information suggests that Ferran used alcoholic beverages rather than ethyl alcohol in preparing his sera. Hernandez (1912²⁸) mentioned that Acosta, at the laboratory of the *Crónica médica-quirúrgica* of Havana, prepared antialcoholic serum as a public service, but no report of Acosta's method has been found.

Bertarelli (1932¹²) stated briefly that antialcoholic horse serum was prepared at the Laboratorio Paulista de Biología (Brazil) by giving horses oral doses of aguardiente until large amounts could be tolerated. After several months the horses were bled and their serum used. He suggested that the serum should be made polyvalent by giving the horses various types of liquors, or that sera should be prepared employing different liquors so that sera homologous to the preferred liquor of the patient would be available, since the alcohol might not be responsible for the effects of the serum—a thought echoed by Carratala.¹⁷ Apparently antialcoholic sera of this type are available in Latin America today, for "*Sôro antialcoólico L.P.B.*" was listed among the biological products available from the Lab-

†No description of this method of increasing the titer could be found, but it was implied to be a chemical method.

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oratorio Paulista de Biologia in 1938,⁶¹ and in 1944 an advertisement for it was interposed in the text of an article on its use by Santiago.⁶⁵

Autosermum^{1,24,38} prepared from the blood of the patient has also been used in Latin America. The patient was instructed to continue ingesting his normal daily amount of alcoholic beverages. Blood was drawn in the morning before the first drink, and the recovered serum was injected subcutaneously or intramuscularly later the same day. This serum was, therefore, similar to that secured from horses given alcoholic beverages but, according to its proponents, it obviated the danger of reactions caused by injection of heterologous serum. Continuing with the idea of avoiding the use of heterologous serum, but with the view that it would be advisable for the patient to cease drinking during the treatment, Pareja C. (1947¹⁷) prepared alcoholized human serum. He withdrew 10 c.c. of blood from the patient and removed the serum from the clot the next day. To 5 c.c. of serum he added 1 c.c. of the alcoholic beverage preferred by the patient and, after shaking and centrifuging the mixture, the supernate was injected intramuscularly. If the serum was not to be used immediately after its preparation, a preservative was added. Later Pareja C.¹⁸ reported that, since it did not seem necessary to practice strict autoserotherapy and because the patients objected to frequent venipuncture, the procedure was modified to making a single withdrawal of 400 c.c. of blood, which provided enough serum for about sixteen injections. He also varied the alcoholic products used for alcoholization of the serum and concluded that aguardiente de caña, of about 36 proof in 30 per cent concentration, produced the best results.

In addition to the various serum preparations for therapeutic use, several investigators have produced serum for experimental purposes only. After waiting for the further reports promised by Toulouse,⁶⁵ Maramaldi¹⁰ decided in 1898 to investigate the two problems Toulouse had proposed, namely, whether the alcohol should be given in more gradual doses over a longer period of time, and whether normal serum would be as effective as antialcoholic serum. Maramaldi began by giving 1 c.c. of 90 per cent ethyl alcohol per kg. of body weight, suitably diluted to prevent local irritation, by stomach tube to a dog; he increased the dose every ten or eleven days. After four months, when the dog was receiving daily doses of about 6 c.c. of alcohol per kg., it was bled. Bleeding was repeated when the animal was receiving about 7.5 c.c. per kg., and it was bled out a few days later after several doses of 8 c.c. per kg. The blood was collected aseptically and kept cold for twenty-four hours before the serum was removed, but no other treatment of the serum was reported.

In 1914 Manoiloff²⁰ reported preparing antialcoholic serum in rabbits for use in the production of passive sensitization to anaphylaxis. Commencing with 0.2 c.c. of 60 per cent alcohol, and increasing the dose by 0.1 c.c. each time, he gave rabbits ethyl alcohol intravenously every other day until a daily dose of 1.5 c.c. was reached. This series of injections was then re-

peated, using next 80 per cent and finally 95 per cent alcohol.* At the end of the third series of injections the rabbits were bled and the serum was inactivated before use.

The most recent reports on production of antialcoholic serum are those of Loiseleur (1946³⁴) and Loiseleur and Levy (1947³⁵), who are studying the antigen-antibody reactions of organic molecules of low molecular weight. They gave injections of 95 per cent ethyl alcohol to rabbits, beginning with 70 mg. of absolute alcohol per day and increasing to a maximum of 7,200 mg. at the end of thirty to forty days. Believing that the difficulty in producing antibodies to molecules of low molecular weight might arise from the rapid excretion of these very small molecules, they used large volumes of diluent, frequent injections, and the intramuscular route to maintain as constant a presence of the antigen in the body as was feasible. In the case of alcohol, each dose was diluted in physiological saline to approximately 30 c.c. and given in two to four equal parts equally spaced throughout twenty-four-hour periods, a procedure designed to make the animals approximate the state of continual alcoholic impregnation encountered in chronic alcoholics. The animals were bled the day after the last injection because it was found that the activity of the serum diminished rapidly once the injections ceased. There was no further processing of the serum, and no mention was made of the effect of storage on its activity. More recently, Loiseleur and Sauvage³⁶ have reported that more satisfactory sera may be produced by twice daily injections of 10 c.c. of a mixture of equal parts absolute ethyl alcohol and physiological saline over a period of ten to twenty days and that the titer of the serum will vary with the length of time the injections are continued. They also reported that the optimal time for bleeding the animals was three to four days after the last injection, a time long enough to allow complete disappearance of free alcohol from the body but not so long that the antibody titer would drop appreciably.

Summary.—The methods of producing antialcoholic sera for therapeutic use appear to have been more haphazard than those for laboratory experimentation, but there is a possibility that methods have been kept secret for commercial reasons. The later reports show a trend toward longer immunization periods and this trend seems practical because such periods usually yield greater amounts of antibody.

There is little reason to criticize the heating of the antialcoholic sera for purposes of inactivation of the complement or for pasteurization, but if Evelyn's "high temperature" was greater than 56° C., it is doubtful that any active antibody remained after heating. If the antialcoholic antibody should be stable at 52° to 56° C., heating the serum was desirable since this would decrease its toxicity.

*It is difficult to believe that these concentrations were actually used, since they would be too injurious to the veins to allow so many injections. Ahlquist⁵ noted that even 20 per cent ethyl alcohol in 5 per cent glucose solution was not satisfactory for repeated intravenous injections.

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TABLE I. PROTOCOL OF MARAMALDI'S EXPERIMENTS*

Weight of Animal g.	Amount 90% Ethyl Alcohol Given	Amount 90% Ethyl Alcohol per kg.	Serum				Observations
			Bleeding	Dose c.c.	Route	Time after Alcohol	
4500	51 c.c.	12 c.c.	May 25	8	Intraperitoneal	3 min.	Cured after 19 hrs.
			May 25	8	Intraperitoneal	3 hrs.	
5000	60 c.c.	12 c.c.	May 25	10	Intraperitoneal	9 hrs.	Cured after 30 hrs.
			May 25	10	Intraperitoneal	4 min.	
6100 6400	79 c.c. 81 c.c.	13 c.c. 13 c.c.	July 6	30†	Intraperitoneal	3 hrs.	Died after 15 hrs. Cured after 30 hrs.
			July 6	15	Subcutaneous	4 min.	
7200	93 c.c.	13 c.c.	July 6	10	Intraperitoneal	3 hrs.	Cured after 22 hrs.
			July 6	10	Subcutaneous	9 hrs.	
7000	98 c.c.	14 c.c.	July 6	10	Intravenous	20½ hrs.	Died after 14 hrs.
			July 6	10	Intraperitoneal	4 min.	
7500	103 c.c.	14 c.c.	July 6	15	Intravenous	40 min.	Cured after 26 hrs.
			July 6	15	Intraperitoneal	5 hrs.	
7300	110 c.c.	15 c.c.	July 18	15	Subcutaneous	5 min.	Cured after 24 hrs.
			July 18	10	Intraperitoneal	3½ hrs.	
6800	100 c.c.	15 c.c.	July 18	10	17½ hrs.	17½ hrs.	Cured after 24 hrs.
			July 18	15	Intraperitoneal	4 min.	
5500 6800	88 c.c. 108 c.c.	16 c.c. 16 c.c.	July 18	10	Intraperitoneal	4½ hrs.	Died after 15 hrs. Died after 18 hrs.
			July 18	40†	Intraperitoneal	50†	
					Intravenous		

*Modified from Table of Maramaldi. (43).

†Only total dose reported.

The severest criticism of most antialcoholic sera produced for therapeutic use is that alcoholic beverages rather than pure ethyl alcohol were employed in their production. This difficulty, intimated by Bertarelli's¹² desire for a polyvalent serum, was better interpreted by Bahamonde Q. (1944¹⁰), who pointed out that some persons have true allergic reactions to certain types of liquors but not to others—reactions which are stimulated by substances other than ethyl alcohol. Thus the use of sera prepared by giving animals liquors does not differentiate between reactions caused by the presence of antibodies to ethyl alcohol and reactions caused by the presence of antibodies to other substances. Hence the only sera that may be considered as possibly having properties derived from the presence of antibodies to ethyl alcohol are those prepared by Toulouse, by Maramaldi, by Sapèlier and his associates, by Manoiloff, and by Loiseleur and his fellow workers. It is unfortunate that Pareja C., who has supplied better case reports and is also the newest author in this field, did not use ethyl alcohol to alcoholize his human serum preparations.

EXPERIMENTAL WORK WITH ANTIALCOHOLIC SERUM

In 1898 Maramaldi⁴⁰ reported the first and best controlled animal experiments with antialcoholic serum. First, he determined the minimal lethal dose of 90 per cent ethyl alcohol for dogs to be 12 c.c. per kg. of body weight when given by stomach tube, and that in all cases death occurred in less than eight hours. He next gave 1 to 1.25 M.L.D. of ethyl alcohol to dogs and three to five minutes later injected the first dose of serum. Additional doses of serum were given at varying intervals (Table I). Of nine dogs thus treated, seven survived. Dogs which received more than 1.25

M.L.D. of alcohol died after fifteen to eighteen hours despite the fact that they were given much larger doses of serum. In all cases death occurred much later in treated animals than in control animals. Finally to demonstrate that the antialcoholic serum was responsible for the survival of the treated animals, 1 M.L.D. of ethyl alcohol was administered to two dogs and then injections of normal serum were made, one being given 40 c.c. and the other 50 c.c. Both dogs developed intoxication of the same intensity and died, as had the control animals, in a little more than three hours. This led Maramaldi to conclude that the antialcoholic serum contained an antitoxin capable of neutralizing the toxic action of 1.25 M.L.D. of ethyl alcohol. He observed that intravenous injection of the serum relieved disturbances of heart rate and respiration more rapidly than intraperitoneal injections, but the duration of the intoxication was the same with either route of administration. Because it was unnecessary to increase the dose of serum appreciably upon increase of the dose of alcohol, Maramaldi assumed that the serum obtained from the later bleedings of the serum-producing dog (used to treat the animals that received the larger doses of alcohol) contained more antitoxin than the earlier lots; he suggested that methods of producing a more potent antitoxin should be investigated.

Three isolated experiments on the use of antialcoholic serum in animals that had been habituated to consuming food or water containing alcohol were cited by Dromard.²² One animal failed to alter its consumption of food or water and two reacted favorably. Sapelier and Dromard²³ mentioned that studies were also made in guinea pigs to observe the effect of the treatment on pregnancy and the resulting progeny, but they did not report any results. The experiments seem to indicate that there was some substance present in the antialcoholic serum which, upon exposure of the treated animals to alcohol, caused a new type of reaction to it—that of avoidance of substances containing alcohol—but the nature of the reaction was not suggested.

In 1914 Manoiloff²⁴ reported that he and Zboromirsky²⁵ apparently had produced anaphylaxis in rabbits and guinea pigs by administering intravenous doses of alcohol forty-eight hours after passive sensitization with serum from chronic alcoholics. This finding led him to prepare an anti-alcoholic rabbit serum which he tested in five rabbits, giving 12 to 15 c.c. of the antiserum intravenously, followed forty-seven to forty-eight hours later by intravenous injection of 0.5 to 0.6 c.c. of 95 per cent ethyl alcohol. Manoiloff stated that all the animals showed typical anaphylactic shock, and his description of postmortem findings in the one animal which died tallies with those usually associated with anaphylaxis in rabbits (Boyd).²⁶ Similar tests in guinea pigs (protocols not reported) gave similar results. He concluded that "serum from alcoholic animals confers passive anaphylaxis."²⁷ As noted earlier, there is some doubt about the actual concentration of ethyl alcohol injected by Manoiloff. If he used 95 per cent

²² *Z. für Physiol. und Physiol.*, 1912, No. 25, pp. 235-237. *Z. für Physiol.*, 1912, No. 25, p. 235. *Z. für Physiol.*, 1912, No. 25, p. 237. *Z. für Physiol.*, 1912, No. 25, p. 237.

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ethyl alcohol for these intravenous injections, it may be questioned whether the rabbit died from right heart failure of anaphylactic origin or from thrombi elicited by the alcohol. This reviewer, however, has injected 95 per cent ethyl alcohol into rabbits intravenously and into guinea pigs intracardially without observing any evidence of thrombus formation during the period when anaphylaxis might be expected to occur. Thus, Manoiloff's conclusions do not seem to be prejudiced by this possibility.

Loiseleur employed the very sensitive method of microviscosimetry, developed by Lecomte du Noüy³⁰ and used for demonstrating diphtheric toxin-antitoxin reactions,³¹ to detect reactions between antialcoholic rabbit serum and ethyl alcohol. He found (1946³¹) as much as 30 per cent increase in the relative viscosity of mixtures of antialcoholic serum and ethyl alcohol over that observed in normal serum-ethyl alcohol mixtures. He also found that if, after the serum of a rabbit showed such an increase in relative viscosity, the animal was given massive doses of alcohol, a decrease in the relative viscosity occurred when tests were done on serum drawn during and just after the administration of the doses, followed by an increase to a new peak. This negative phase in the relative viscosity curve, Loiseleur believed, corresponded to a temporary *in vivo* neutralization of the active principle by the excessive dose of antigen. In 1947 Loiseleur and Levy³² reported that they had found the zone of equivalence for the maximum relative viscosity of antialcoholic serum-ethyl alcohol mixtures to be at a concentration of 0.1 mg. of absolute alcohol per cubic centimeter of serum, and that fractionation of the serum revealed that the active principle was associated with the pseudoglobulin fraction. They also found that there was considerable specificity in the reaction, for when serum, from animals injected with ethyl alcohol, was tested with methyl alcohol, the peak in the curve of relative viscosity measurements was less than one-half that with ethyl alcohol and the zone of equivalence fell at about 0.05 mg. per cubic centimeter of serum. It is interesting that in a similar study done with morphine there was also an increase in the relative viscosity of antimorphine serum-morphine mixtures as the administration of morphine proceeded; however, when massive doses of morphine were given, the relative viscosity continued to increase without any evidence of temporary *in vivo* neutralization by excess antigen. In a later paper, Loiseleur and Sauvage (1948³³) reported that when gamma globulin, prepared from antialcoholic serum, was tested, opacity occurred in mixtures representing the zone of equivalence, and that the specificity of the reaction extended to propyl as well as to methyl alcohol.*

Loiseleur and Levy³⁵ speculated that physiological need (*besoin*) for both of these drugs may arise from the presence of the "antibodies" (*anticorps*) which they reported, and that therapy for such addictions may someday be achieved through the production of "anti-antibodies" (*contre-anticorps*) which would allay such need. This speculation was repeated by

*Reviewer's translation.

Loiseleur and Sauvage, who referred also to the work of Bruel and Lecoq with intravenous administration of alcohol for the relief of symptoms associated with chronic alcoholism. Since they do not explain how unbound "antibody" can cause need for the homologous antigen, and since it is more probable that an antigen-antibody or antigen-reagin complex may exist in alcoholics (at least while they are drinking), this speculation is hard to justify. A more conservative postulate would be that some abnormal reactions to these drugs arise from the formation of a reagin which, in combination with the antigen, elicits an allergic reaction (in this case the reagin shows *in vitro* reactions); or since it was not shown that the response of the rabbits to alcohol was abnormal, it may be that their serum contained an antibody and that a different mechanism is involved in abnormal physiological reactions to alcohol. Until sera from non-drinkers and from normal and abnormal drinkers are studied under the same conditions, no conclusions can be drawn about the role of the active principle described by Loiseleur in alcoholism.

Summary.—The seemingly clear-cut findings of Maramaldi, Manioloff and Loiseleur, suggesting that antialcoholic serum has some peculiar properties, necessitates confirmation of the findings and determination whether the properties are of protective (Maramaldi) or allergic (Manioloff) character, or whether the conditions of the preparation of the serum determine its character. Such confirmation might explain the nature of tolerance to alcohol, or the altered response to alcohol, observed in chronic alcoholism, which at times resembles the development of hypersensitivity reactions. Rosenfeld (1914⁵⁴), who studied tolerance to methyl and ethyl alcohol, did not find any increase in resistance to lethal doses of methyl alcohol after animals had been habituated to ethyl alcohol, or vice versa. This phenomenon is in accord with Loiseleur's claim of specificity for his anti-alcoholic serum.

THERAPEUTIC USE OF ANTIALCOHOLIC SERUM

In 1896 Toulouse^{64,65} administered antialcoholic dog serum to a patient suffering from acute alcoholism with delirium tremens and found that the patient recovered more easily than was usual in such cases. The accounts of Evelyn's^{18,52} use of Equinine are rather incomplete. Apparently a disk was moistened with sterile water and applied to the skin of the patient after scarification in the manner employed for smallpox vaccination. When the disk lost its color, due to absorption of the serum, a fresh disk was applied to the same area. The patient was said to lose his taste for alcohol after seven or eight applications.

From 1900 to 1903 antialcoholic serotherapy was developed by a group working with Sapelier in France. In 1900 Thébault⁶² reported thirty-three

*In a personal communication, Loiseleur stated that if the mixtures of antialcoholic serum and ethyl alcohol used for the viscosimetric measurements, are incubated at 40° to 50° C. overnight, precipitation will occur, and that usually the maximum amount of precipitation will occur in the mixture representing the zone of equivalence.

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successes and eight improvements in fifty-seven trials.** Dromard (1902²²) reported success in all of thirty patients considered suitable for treatment and failure in all of ten deemed unsuitable. This French group differed from Toulouse in that they were interested in curing addiction to alcohol rather than relieving the acute symptoms of alcoholic intoxication.⁵⁶ They found the best field for this to be among latent alcoholics, or (in their term) "alcoholomaniacs," who suffered from physiological need (*accoutumance et besoin*) but did not yet show clinical evidence of the toxic effects of alcohol. In such patients, if the treatment was completed, antialcoholic serotherapy produced such a degree of repulsion and distaste for alcoholic beverages that even the sight or odor of liquor stimulated pallor, sweating, faintness, nausea and vomiting.

To account for the existence of what we call tolerance, Sapelier and Dromard postulated that alcohol possessed two active parts: one corresponding to Ehrlich's haptophore group and the other corresponding to his toxaphore group. Upon entrance of alcohol into a cell, the haptophore group was believed to cause alteration of the cell's metabolism to include production of receptors or antibodies for the protection of the cell from the toxophore group. When hyperproduction occurred, the excess receptors were released into the blood stream with resultant immunity, or tolerance, to alcohol. They thought that when the cells became accustomed to producing the antibody their metabolism was so altered that they became dependent on alcohol for nourishment, and that this nutritional requirement was the basis of physiological need. Administration of antialcoholic serum to a patient was presumed to cause the cells possessing this abnormal requirement to revert to their normal requirements, with concomitant loss of tolerance and physiological need and with re-establishment of the repulsion and distaste for alcohol which they considered the normal (non-drinker) reaction to alcohol. This explanation is weak for two reasons. First, tolerance to alcohol is considered to occur only in abnormal drinkers and is linked with physiological need. Second, in the alcoholic individual alcohol is presumed to induce the formation of an antibody responsible for immunity to the effects of alcohol, while administration of a serum prepared by giving animals alcohol results in cessation of antibody production and loss of immunity.

Of course, if more alcohol had been ingested than could be neutralized by the receptors produced by the cells, it elicited organic lesions. When this had occurred, Sapelier and Dromard felt that serotherapy was futile, because it could not be expected to restore cells which had been destroyed by the toxophore group. The duration of the repulsion varied, lasting for at least a year in some cases; but if the patient was unco-operative and forced himself to drink, the repulsion soon disappeared and relapse, accompanied by the return of physiological need for alcohol, occurred. They believed

**An identical set of figures was attributed to a report by Broca-Soucellier, Sapelier and Thébault by the editor of *Le Concours Médical*,²⁰ and was repeated by Thébault in 1901.⁶³ These reports apparently represent the same data.

that the occurrence of a relapse after antialcoholic serotherapy was no more valid criticism of the serum than a second attack of an infectious disease, following serotherapy for relief of the primary attack, would be of the value of the latter serum.

Sapelier and Dromard noted that serotherapy was less effective in wine drinkers than in drinkers of hard liquor; they attributed this to the fact that wine apparently more often incited digestive disorders than did other types of liquor. They did not recommend serotherapy in cases of dipsomania, other psychoses, or alcoholism associated with organic disease whether of alcoholic or nonalcoholic origin (tuberculosis, syphilis, et cetera), because alcohol or other agents had already caused irreparable damage. It is interesting to note that none of the thirty-four patients with such complications treated by Thébault²² or Dromard²² responded to serotherapy even though they received much more than the usual amount of serum. Sapelier and Dromard²² particularly emphasized that suggestion had no part in the development of the repulsion, for suggestible patients uniformly exhibited little or no improvement while suitable patients who did not know that the treatment was directed toward their alcoholism developed repulsion satisfactorily. It should be noted that these authors treated chronic alcoholism on a purely physiological basis and found that their treatment was unsatisfactory when alcoholism was associated with psychotic states (dipsomania was considered to be a psychosis), i.e., the alcoholism probably was a secondary disease.

The book by Sapelier and Dromard²² on the selection of patients and the mechanism of the reaction seems to have been responsible for the spread of the method to Spain and Latin America.^{2,12,21,28} Table II summarizes the available case reports recorded since 1896.†

Use of antialcoholic horse serum has predominated, but several other preparations which might well carry a similar active principle have been employed. Hernandez,²⁸ while using reinjection of ascitic fluid obtained by paracentesis to treat a patient for hypertrophy of the liver with hydropoietic ascites, obtained not only an improvement of the ascites but the development of a repulsion to alcohol which resulted in the patient's abstinence until the date of the report several months later. It is interesting that Hernandez based his treatment of the ascites on the method of Galup,²⁶ who worked in Paris soon after Sapelier, but did not record the observation of any change in the drinking habits of patients after this treatment for ascites associated with chronic alcoholism.

Autohemotherapy^{21,38,41,68} and autoserotherapy¹ seem to have yielded results comparable to those obtained with heterologous serum, although Wolffenbüttel,⁶⁸ Martimor and Maillefer⁴¹ and Acevedo Castillo¹ reinforced the action of autohemotherapy or autoserotherapy by the use of ipecac or some other vomitant. These reports seem to contradict the find-

†More case histories probably have been published in Latin America, especially in the *Archivos de Biología*, but they have not been cited in American indices and the journals are not available for search. It is believed, however, that those cited may be considered typical.

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TABLE II. RESULTS OF SEROTHERAPY IN CHRONIC ALCOHOLISM

Author	Date	Type of Serum	No. of Cases	Results Reported	Comment
Thebault ²²	1900	Horse (prepared with ethyl alcohol)	57	33 successful 8 improved (1 did not finish treatment, 4 showed contraindications) 16 failures (4 did not finish treatment, 13 showed contraindication ^a)	Period of observation not stated
Dromard ²²	1902	Same	30	30 successful (all latent alcoholics)	Max. period obs 12 mo, median 4 mo, 11 relapsed at varying intervals. Some able to drink moderately at time of last report
Acosta ^{23, 24}	1904 1905 1907	Horse (preparation not known)	10 90	10 unsuccessful (all showed contraindications to treatment) 70 cured and confirmed 13 extent of cure not confirmed 7 excluded (uncooperative, did not finish treatment)	Period of observation not stated, 1 year in some cases
Blasco ²⁵	1905	Horse	8	2 cured, 8 mo after inj. 1 cured 2 mo after inj., relapsed and retreated less successfully 1 cured, relapsed at 8 mo but drank more moderately 4 failures (1 relapsed at 8 mo, 2 abandoned treatment, 1 received serum orally)	
Hernandez ²⁶	1912	Ascitic fluid	1	1 cured (about 9 mo. after treatment)	
Escomel ²⁷	1928	Autohemotherapy	1	1 cured	Period of observation not stated
López Lomba ²⁸	1932	Same	24	23 successful	Period of observation not stated
Wolffenbuttel ²⁹	1935	Same, plus tartar emetic, ipecac, hyposis	24	22 successful 1 abstinent for 8 years 1 abstinent for 4 months	
Martumcr & Maillefer ³⁰	1936	Autohemotherapy	11	5 successful	Period of observation not stated
Martinez ³¹	1937	Same plus ipecac	45	40 successful	Period of observation not stated
Martinez ³²	1937	Soro anti-alcoólico L. P. B.	1	1 cured—observed 2 months	
Quintero ³³	1937	Same	2	2 cured—observed 1 month	
Freire ³³	1937	Same	2	2 cured—observed 5 months	Period of observation not stated
Ribeiro ³³	1937	Same	1	1 cured—observed 2 years	Period of observation not stated
Schulhof ³³	1938	Same	1	1 cured	
Elizondo ³³	1938	Same	1	1 cured	Period of observation not stated
Acevedo Castillo ³⁴	1943	Autosero-therapy	16	7 cured (considered method a conditioned reflex treatment) 4 improved 4 failures	Period of observation not stated for each patient, range 1-14 months
Santiago ³⁵	1944	Soro anti-alcoólico L. P. B.	2	1 under treatment 1 cured (abstinent) 1 improved (drinks occasionally but can work)	Period of observation not stated
Miro ³⁵	1944	Same	1	1 cured	Period of observation not stated
Pareja C. ³⁷	1947	Alcoholized human serum	16	9 cured—most cases observed 3 months 3 improved at end of treatment (2 for about 8 months) 4 failures	
Pareja C. ³⁸	1947	Same	111	61 definitely abstemious 21 improved 6 failures 23 abandoned treatment	Period of observation not stated

ings of Sapelier and his associates that chronic alcoholics with clinical evidence of damage from alcohol, dipsomaniacs, and the like are not benefited by serotherapy. In fact, none of the more detailed case histories indicate treatment of the mild form of addiction—latent alcoholism—and many definitely mention the presence of dipsomania or hepatic dysfunction in patients successfully treated.

The procedure in most of these methods was to permit the patient to continue his normal drinking pattern, allowing cessation of drinking to occur naturally with the development of repulsion or distaste for alcohol. Sapelier and Dromard⁵⁶ stated that it was important to allow the patient to continue his exposure to temptation, but did not definitely say that continued ingestion of alcohol was necessary or had any part in the effectiveness of the serum. In many cases patients voluntarily ceased drinking after their first injection, but were treated for some time longer; and often those who required the largest amount of serum to stop their drinking relapsed the soonest. A possible clue to the part played by alcohol in serotherapy is found in the reports of Pareja C.^{47,48} who did not believe that it was right for the patient to continue drinking during the treatment. Instead, he used intramuscular injections of alcoholized patient's serum to produce the repulsion. This seems to indicate that the active element in this type of treatment may be either (1) an antigen-reagin complex which stimulates formation of the "anti-antibody" postulated by Loiseleur and Levy,³⁵ or (2) a protein-alcohol complex which reacts with a reagin to produce a more severe response than that produced by the formation of a similar *in vivo* protein-alcohol complex, possibly because the response is not masked by the narcotic effects of alcohol.

Summary.—The reports of the therapists who employed ipecac or apomorphine in conjunction with serotherapy must be disregarded, since these drugs alone cause nausea and vomiting and since their use makes such methods of treatment similar to the conditioned-reflex method of Voegtlin.⁶⁶ Toulouse's report of the effect of serum in acute alcoholism, however, suggests that it has protective properties and the rest of the reports suggest that serum from animals or persons who have undergone prolonged exposure to ethyl alcohol, or to substances containing it, develops a substance which, either alone or in the presence of ethyl alcohol, is capable of producing repulsion to alcohol in those addicted to its use. To date the exact mechanism of these reactions has not been investigated.

DISCUSSION

Considering the great interest that has been consistently displayed in the problem of alcoholism, it is remarkable that the experimental studies with antialcoholic serum have not been repeated under conditions which would test the validity of the claims that an alcoholic antibody or reagin may develop in the serum of animals or persons exposed to ethyl alcohol. Moreover, although the alcohol susceptibility skin test has been presumed to involve an immunological concept, no study of its mechanism or relationship to other reports of immunological reactions to alcohol has been made. The following discussion is an attempt to clarify thinking on the mechanisms which may be involved in the diverse results reported, so that the direction of further study may be more readily seen.

Correlation of Perlman's^{19,50} and Haxthausen's²⁷ reports of cutaneous hypersensitivity to ethyl alcohol with Manoiloff's³⁹ report of anaphylaxis

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to alcohol following passive sensitization with antialcoholic serum suggests that a substance having the properties of a reagin may exist. The phenomenon of repulsion and gastric revolt reported to be produced by antialcoholic serum in subjects habituated to alcohol would seem to indicate that the serum may contain an antialcoholic reagin, and that its administration may increase the reagin titer sufficiently to elicit a hypersensitivity reaction of such severity that the subject is restrained from drinking. On this basis, tolerance might exist when a subject does not produce a reagin to alcohol and susceptibility when he does produce one. Thus, susceptibility, whether acquired or inherited, would be an abnormal state similar to allergy and, like allergy, most easily controlled by avoidance of the causative agent.

The foregoing, however, does not account for intolerance to alcohol or for the increase of tolerance which usually occurs after experience in drinking (even when drinking is irregular). This situation would be better met by an explanation arising from the reports of Toulouse^{63,64} and Maramaldi⁴⁰ that the active principle in antialcoholic serum acts as a specifically neutralizing antibody. Should this be the case, the explanation of tolerance would be reversed, for the presence of the antibody should provide protection or tolerance and its absence should cause intolerance. The alcohol susceptibility skin test does not, at present, influence either this or the previously postulated explanation of the response, for it does not differentiate between tolerance and susceptibility to alcohol. It appears to be more like the Schick test than like a skin test for allergy, but does not indicate whether "immunity" to alcohol involves a positive adaptation such as the formation of an antibody or just a negative adaptation of the body to alcohol (disregard for its presence).

By recognizing that reagin formation does not preclude antibody formation,⁴⁴ a more probable explanation appears. This is that both antibody and reagin production may occur in response to alcohol, with normal antibody formation representing the normal reaction—development of tolerance upon exposure to alcohol; lack of antibody formation (whether due to lack of exposure or failure to respond normally) representing intolerance; and abnormal antibody or reagin formation accounting for allergic reactions and possibly for some of the abnormal reactions of chronic alcoholics to alcohol. Whether alcohol alone may be antigenic or whether it may become antigenic only after combining with a protein to form a hapten has not yet been determined. The *in vitro* reactions obtained by Loiseleur³⁵ suggest but do not prove that it is a complete antigen. A "hapten theory" would make explanation of the existence of both antibody and reagin formation simpler, particularly if it could be shown that the form of the protein involved varies or that two or more proteins are involved.

Thus far this discussion has emphasized the relationship of a theoretical antigenic activity of alcohol to tolerance to alcohol; and of a theoretical reagin which, in combination with alcohol, might account for clear-cut

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manifestations of allergy to alcohol. It is also necessary to consider the role of such a reagin in physiological need for alcohol.* As pointed out before, it is difficult to see how an antigen-reagin complex could cause a demand for the presence of more alcohol to alleviate its toxic effects, particularly the large quantities of alcohol which are demanded. The only possible explanation which can connect the existence of an antigen-reagin complex with physiological need is that the toxic effects of the complex are dulled by the normal sedative effect of alcohol. While it may be objected that, under such conditions, the sedative effect of alcohol would be sought for psychological rather than physiological reasons, it must be pointed out that Bruel and Lecoq¹⁶ and others** have repeatedly said that intravenous injection of alcohol causes dramatic relief of delirium tremens. Oral administration of alcohol does not give this result and no other sedative acts in such a specific manner. Similarly Bruel and Lecoq found that intravenous administration of alcohol prevents the occurrence of withdrawal symptoms on abrupt cessation of drinking but that no permanent desensitization to oral ingestion of alcohol occurred. As a whole these findings tend to discourage the idea that any allergic reaction is involved in abnormal responses to alcohol by chronic alcoholics, but it may be that the unusual route of administration precluded formation of any toxic antigen-reagin complex.

In conclusion it may be said that in chronic alcoholism we have a situation wherein an apparently permanent sensitization to alcohol occurs which, at present, is relieved only by absolute and permanent cessation of contact with alcohol, including involuntary contact through such media as cough medicines and elixirs. The reports herein reviewed suggest that in some cases the sensitization may be similar to allergy and seem to warrant investigation of the following questions:

1. Does alcohol, either alone or in combination with some protein, function as an antigen or allergen?
2. If so, what are the properties of any antibody or reagin so formed?
(1) What is the explanation of the sensitizing action of antialcoholic serum reported to have occurred both in animals and in chronic alcoholics?
(2) What is the explanation of the therapeutic action of antialcoholic serum reported to have occurred in acute alcoholism?
3. Is the alcohol susceptibility skin test a measure of tolerance or of susceptibility, and what is its mechanism?
4. What is the mechanism of the beneficial results of intravenous administration of ethyl alcohol in delirium tremens?

*There is much discussion as to whether physiological need for alcohol exists, particularly because no satisfactory explanation for its existence has been offered. Williams, Berry and Beertseher¹⁷ have reported, within the last few months, that in rats and mice they have found distinctive genetic differences in response to alcohol consumption and that in certain strains of animals and certain individual animals it is relatively difficult to reduce alcohol consumption. They stated that clear evidence had been obtained that the creation of an appetite for alcohol in these animals is due to different deficiencies and that the basis of alcoholism might possibly be nutritional.

**Personal communications.

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If and when any or all of these questions are answered, we shall have a basis for confirming or denying the validity of the reports of the various immunological properties of alcohol, as well as considerably more insight into the physiological portion of the problem of alcoholism.

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NORISODRINE SULPHATE (25 PER CENT) DUST INHALATION IN SEVERE ASTHMA

HARRY SWARTZ, M.D., F.A.C.A.

New York, New York

SINCE the advent of epinephrine and ephedrine as adjuvants in the therapy of asthma, the search has proceeded for more effective agents productive of fewer side-effects. When, in the last decade, reports on related compounds appeared in the European literature^{1,2,5,8,11,14} and later in the American literature, much interest was stirred among allergists. Encouraging reports concerning one such drug, Isopropylarterenol Sulphate, commonly known as Norisodrine Sulphate have appeared in this country since 1947.^{3,4,6,7,10,12} A most interesting feature of these reports was the efficacy of this drug in the severe asthmatics who were often refractory to other symptomatic medication.

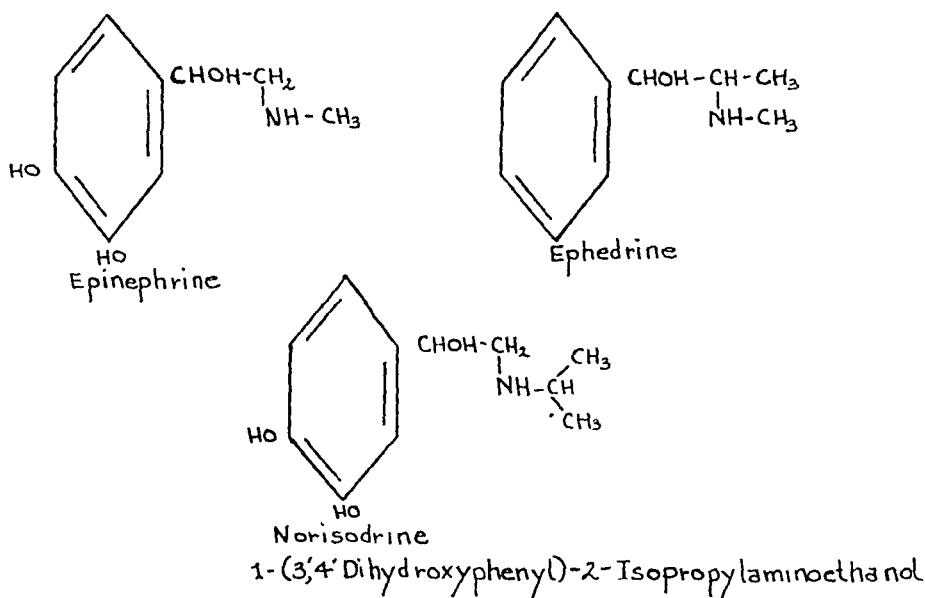


Fig. 1

The purpose of this paper is to present the results of symptomatic treatment of a dozen severe asthmatics with Norisodrine. Although this is a small number of cases from which to draw true conclusions, it is felt it will add a fragment to the accumulating data concerning the drug.

Like epinephrine, Norisodrine is a dihydroxyphenyl-ethanol amine. It differs from the former only in its alkyl group, being the isopropyl homologue of epinephrine. The structural formulas of epinephrine, ephedrine and Norisodrine are reproduced in Figure 1 for comparison.

By laboratory experiment, Norisodrine has been shown to be far less

Norisodrine Sulphate, 25 per cent Sister Cartridges and Aerohalors were kindly supplied by the Abbott Laboratories.

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toxic than epinephrine and to have a much greater broncho-dilating effect.^{9,13}

Norisodrine has been used orally, subcutaneously, by hand nebulizer and dust inhalation. It was felt that for the ambulatory severe asthmatic the choice method of administration was dust inhalation (25 per cent). It is less cumbersome than hand nebulization or self injection; its effect is more rapid than the tablet; the small plastic inhaler is easily carried on the person, is unbreakable and with a little adeptness can be used in public unnoticed.

The patients selected for trial therapy were those whose treatment had been unsatisfactory in the past, whose symptoms had persisted for a long period of time and/or whose response to the more common anti-asthmatic drugs was minimal. For the most part, these cases belonged to that group so well known in every allergist's office, refractory to treatment. In addition, four mild cases of asthma were included for comparison of result. These were adequately attack-controlled by the ordinary medicaments such as epinephrine, ephedrine, aminophylline, iodides, antihistaminics alone or in combination.

Table I is an analysis of the patients and the results of treatment.

As is seen from this table, the patients ranged in age from twenty-nine to seventy. Extrinsic, intrinsic and combined types of asthma are represented. The duration of asthma was from two to thirty years, and the attack-frequency and severity were great enough to interfere seriously with the patient's day-to-day functioning. Almost all of these patients did not respond well to the more common anti-asthmatic drugs.

Of the twelve patients with severe asthma, nine experienced prolonged freedom from symptoms within a few minutes of two or three inhalations, without side effects. This was considered an excellent result. One showed a tendency to need more Norisodrine as time went on and experienced an occasional moment of palpitation, but prolonged rapid relief was obtained. This was considered a very good result. Another patient required five inhalations and the effect was not noted for ten minutes. But once relief set in, it was of considerable duration. This too was considered a good result. Another patient who responded very well to nebulized epinephrine needed two series of three inhalations of Norisodrine for relief. The effect was noticeable only after a ten-minute interval, and with it, he experienced some nausea. This patient also showed a tendency to need a greater number of inhalations as time progressed. This was considered only a fair result.

In several instances, the patient was able to discard routine daily epinephrine injections and rely on Norisodrine. This was of great benefit psychologically and from the point of view of work capacity. Dust inhalation was a matter of a few seconds and could be done in an inconspicuous manner. This obviated the former necessity of leaving the job for an injection, waiting for relief and the disappearance of side effects.

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TABLE I.

Type of Asthma	Age Sex	Attack Duration	Response to Other Drugs	Epinephrine	Complication	Phenyldimethyl Benzylamine Ephedrine	Response to Norisodrine (25%)		Period of Treat- ment	Inc. Toler- ance	Results	Comment	
							No. Inhalations	Time before Relief					
1 F 40	X	4	3/Wk.	24 to 48 Hrs.	Menopause & Emotional Instability	Good and Marked Palpitation	Neg.	3	2' Aborts Attack	None	3 Mos.	None	Excel.
2 M 44	X	3	Daily	6 to 8 Hrs.	—	Fast	Neg.	I. V. Fair	4' 5' 4 Hrs.	None	3 Mos.	None	Excel.
3 F 38 X	20	2/Wk.	Anxiety Neurosis	3 to 4 Days	—	Fast	Neg.	I. V. Fair	3' 6 Hrs.	None	3 Mos.	None	Excel.
4 M 53	X	15	1/Wk.	2 Days	—	S. C. Marked Tachy. Inh. Neg. Good	Neg.	I. V. Fair	3' 2'	8-10 Hrs. Occlus., Palpitation	2 Mos.	Recently Inc. to 4 Inhal. Inhal.	Very Good
5 M 59	X	11	1/10 Days	12 Hrs.	G. B. Disease	Marked tachycardia S. C.	Neg.	Neg.	10' 3 Hrs.	Nausea	2 Mos.	None	Fair
6 M 46	X	7	On Exertion	10' to 3 Hrs.	Bronchi- ectasis	Marked tachycardia S. C.	Neg.	I. V. Good	2' 2'	Aborts Attack	Neg.	2 1/2 Mos.	Good
7 M 51	X	5	82 Wks.	2 Days	G. I. Allergy	Good Side Effects	Neg.	I. V. Good	2' 2'	Aborts Attack	Neg.	2 Mos.	Excel.
8 F 29 X	15	more in Pol. Sea'n	2 to 3 Weeks	1 Day	—	Good S. C.	Neg.	I. V. Good	3' 10 to 12 Hrs.	Aborts Attack	Neg.	2 Mos.	None
9 F 30 X	5	8 Week	—	—	—	Good S. C.	Neg.	I. V. Good	2' 2'	Aborts Attack	Neg.	3 Mos.	None
10 M 36 X	4	Daily	10 to 14 Hrs.	—	—	Good S. C.	Neg.	I. V. Good	3' 10 to 12 Hrs.	Aborts Attack	Neg.	3 Mos.	None
11 M 45 X	2	8 Month	7 to 10 Days	Hypothyroid	—	Good S. C.	Neg.	I. V. Good	4' 5'	10 to 12 Hrs.	Neg.	2 Mos.	None
12 F 70	X	30	Daily	—	—	Good Fast	Neg.	I. V. Good	4' 5-7'	4 to 6 Hrs. Palpitation	Mild	2 Mos.	Excel.
MILD ASTHMA (Control)												—	Unsatisfactory
1 F 22 X	2	8 Weeks	2 to 3 Weekly	4 to 5 Hrs.	—	Excel.	Good	Good	—	—	2 Mos.	—	Unsatisfactory
2 F 31 X	1	6 to 8 Hrs.	—	—	—	Excell.	Excell.	Excell.	—	—	2 Mos.	—	Unsatisfactory
3 M 39	X	3 Weekly	—	—	—	Excell.	Excell.	Excell.	—	—	2 Mos.	—	Unsatisfactory
4	4	2/Wk.	6 to 7 Hrs.	—	—	Excell.	Excell.	Excell.	3' 2'	—	2 Mos.	None	Excel.

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Where the patients ordinarily had recourse to intravenous aminophylline, Norisodrine inhalation obviated the need for a relatively complex procedure requiring the physician's care and gave the patient a much greater sense of security.

In Patient 1, who was suffering menopausal symptoms as well as asthma, Norisodrine aborted the "flush"-attached attack and seemed to prevent attacks that arose after the ingestion of hormone.

In Patient 6, whose asthma was complicated by bronchiectasis, use of Norisodrine not only relieved the paroxysm but also resulted in a copious flow of secretion.

It is interesting to note that in Patient 7, whose asthma was complicated by bouts of abdominal pain, eructation and nausea, Norisodrine relieved not only the asthmatic attack but also the gastrointestinal symptoms. These latter also had occurred independent of the asthmatic paroxysms but had disappeared almost entirely during the period of Norisodrine usage.

It should be stressed that during the period of Norisodrine use, none of these patients was given any other medication. Specific therapy alone was continued.

In the group of four mild to moderate asthmatic patients, all of whom responded well to epinephrine, ephedrine, antihistaminics and/or aminophylline, Norisodrine was ineffective in three, gave an excellent result in one.

Dosage of Norisodrine dust is an individual matter and is determined with each patient specifically. During the course of symptoms, the patient is instructed to take two or three shallow inhalations. Careful watch is kept for time of onset of relief and completeness of relief. If necessary an adjustment is made in the number of inhalations. Once this test dose is determined, the patient is instructed to use this dosage and no more at the earliest sign of symptoms. It is important to emphasize shallow inhalations. Deep inhalations may lead to overdosage and side effects of severity since the drug is a powerful sympathomimetic.

On the basis of the obvious disparity in results of Norisodrine therapy in the comparatively mild asthmatics and the severe asthmatics, it can be postulated that the efficacy of the drug is based primarily on its bronchodilating effect. Conversely, it might be assumed that its effect on bronchomucosal edema is minimal. The foundation for these assumptions is, first, that bronchospasm is more apt to play a major role in the asthmatic attack where the condition is of long standing or great severity and, second, upon the laboratory demonstration of the marked broncho-dilating effect of the drug. In the early or mild asthmatic, mucosal edema is more apt to be the underlying mechanism of dyspnea and therefore, here, Norisodrine is less effective.

In summary, it can be said that Norisodrine is an unusually effective symptomatic therapeutic for severe asthma when inhaled as a dust. It

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gives relief to epinephrine-fast asthmatics and those refractory to other anti-asthmatics. Under controlled conditions, there are few side-effects and little evidence of increasing tolerance.

105 East 73rd Street

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FLORIDA ALLERGY SOCIETY

We are very pleased to announce the formation of an allergy section of the Florida Medical Association known as the Florida Allergy Society. Officers for the present year are Dr. Clarence Bernstein of Orlando, President; Dr. Frederick Hieber of St. Petersburg, Vice-president and President-elect; and Dr. Nelson Zivitz of Miami Beach, Secretary-treasurer. Besides these officers, other charter members are Drs. Frank Metzger of Tampa, S. D. Klotz of Orlando, M. J. Flipse, Edwin D. Preston, James Putnam and Harold Rand of Miami, Louis Palay of Miami Beach, Frederick D. Droege of Sarasota, W. H. Gardner of West Palm Beach, J. M. McDonald of Jacksonville, and Claude Frazier, location pending. Dr. W. Ambrose McGee of Richmond, Virginia, was elected a new honorary member. At the organization meeting, April 23, Dr. S. D. Klotz presented a paper entitled "Allergy and the Heart," which was published in the May-June issue of ANNALS OF ALLERGY.

MODIFIED ANTIHISTAMINIC OINTMENT

Its Topical Use in the Treatment of Pruritus

FRANK C. COMBES, M.D., ORLANDO CANIZARES, M.D..

and

ERWIN DI CYAN, Ph.D.

New York, New York

PRURITUS is the predominant subjective symptom in most cutaneous diseases. Unlike pain, its control cannot be satisfactorily accomplished by analgesics. Local applications which heighten the threshold of receptivity of the receptor organs of the skin ameliorate and often abolish pruritus. Also, for topical effect other mechanisms of action have been described. With the introduction of antihistaminic drugs there have become available a group of agents, the mechanism of action of which is believed to be a blocking of histamine elaboration, or a blocking of the combination of histamine with tissue cells. This has led several investigators to use antihistaminic drugs locally on pruritic eruptions. In such instances, their topical application has been shown to reduce the wheal reaction produced by application of histamine to the skin.² By local use, their benefits could be obtained without the untoward effects which often accompany oral administration (drowsiness, nausea, etc.). Among the investigators who have found the use of topical application of antihistamines satisfactory are Feinberg and Bernstein,¹ Orecklin,³ Woolridge and Joseph,⁵ and Sulzberger, Baer and Levin.⁴ Most investigators have found them of value in circumscribed neurodermatitis and anogenital pruritus, as well as contact dermatitis due to poison ivy and insect bites.

On the theory that a combination of an antihistaminic drug with other agents believed to ameliorate pruritus may be productive of more rapid effect, there was selected by us for clinical trial an ointment* consisting of 2 per cent methapyriline hydrochloride with 10 per cent calmitol liquid** in a water-miscible base composed of stearyl alcohol, carbowax, sodium lauryl sulfates, and water.

DATA

Our clinical material consisted of seventy-five patients with various dermatoses, from private practice and from the out-patient clinic and dermatologic wards of Bellevue Hospital. Calthenamine ®, the modified antihistaminic ointment, was gently applied to the affected areas three times daily. Those patients exhibiting bilateral and symmetrical

From the Department of Dermatology and the New York University Post-graduate Medical School (Dr. Mario B. and the Service of Dermatology and Syphilology of Bellevue Hospital (Dr. Chief of Service).

Dr. Di Cyan is Director, Di Cyan & Brown, Consulting Chemists, New York.

*This was supplied under its trade name CALTHENAMINE CREAM by Thomas Leeming & Co., Inc., New York.

**Calmitol liquid is composed of, per fl. oz.: Hyoscyamine Oleate 0.006 gr. (equiv. to Hyoscyamine alkaloid 0.003 gr.) chloral 1.29 gm., menthol 1.73 gm., camphor 1.64 gm., alcohol 14.3 c.c., ether 5.1 c.c. and chloroform 1.9 c.c.

lesions were also used as controls, a control ointment consisting purely of the water-miscible base and free of active ingredients being applied to the left side and Calthenamine to the right side.

The results were classified into three groups, i.e., *excellent*, *satisfactory*, and *failures*. In the *excellent* group were included those cases in which the response was both rapid and/or completely successful. In this group, the pruritus was mitigated or disappeared, sometimes in a few minutes, as in the case of insect bites. In some instances the pruritus disappeared with only one application and did not recur. In others, the relief lasted for a few hours, and upon reapplication of the ointment relief continued. In some patients in this *excellent* group, such as those with localized neurodermatitis (which is perpetuated by scratching), the cessation of pruritus led to rapid improvement of the lesions.

In the *satisfactory* group were included cases in which the pruritus was mitigated, but less consistently so, or for shorter periods than in the excellent group.

In some instances designated either as *excellent* or *satisfactory*, the itching recurred, since there was no amelioration of the dermatitis proper.

In the group of *failures* were included those patients who failed to respond to the modified antihistaminic ointment. In two cases the lesions were aggravated.

Urticaria.—Urticarias were divided into two groups: those due to insect bites and those due to other causes. Of six cases of insect bites, five were treated with excellent results and one failed to respond. In the successful cases the pruritus subsided, often within fifteen minutes of application. Of five cases of urticaria due to other causes (penicillin, physical allergy, etc.) one was treated with excellent results, three with satisfactory results, and one failed to respond.

Dermatitis Venenata (Contact Dermatitis).—This entity was divided into two groups. One group included contact dermatitis due to plants (poison ivy, etc.); the other included contact dermatitis due to substances other than plants. In the plant group, of eight cases of poison ivy dermatitis treated, five responded with excellent results and three failed to respond. These latter were acute cases in the vesicular stage. Those that responded favorably were cases in which the acute stage had subsided with wet dressings of boric acid or saline solution, for the treatment of the lesions proper as independent from the treatment of the pruritus. In dermatitis venenata of other than plant origin (the largest entity), the etiology of the eruptions and their location varied. In some instances the eruptions were due to contact with irritants handled in the patients' work; in others the causative agents were cleansing substances (soap, et cetera) or drugs. In a few cases, the offending agent could not be

determined. In this group of thirty-two patients with dermatitis venenata, eight responded excellently, fifteen satisfactorily, and nine were classed as failures.

Disseminate Neurodermatitis (Atopic Eczema).—Of eight patients treated, three obtained satisfactory relief from pruritus; pruritus recurred in two patients after a period of about two weeks. It is interesting to note that of the five failures, two obtained relief with Calthenamine base used as a control.

Localized Neurodermatitis.—Of five patients treated, two obtained excellent results: the pruritus completely disappeared and the lesions underwent rapid involution. In three the results were satisfactory, for the pruritus disappeared but the lesions were not modified. All lesions in this group were of long standing.

Anogenital Pruritus.—Of nine patients treated, only one excellent result was obtained; in four the results were satisfactory, and four failed to respond.

Miliaria (Prickly Heat).—Two patients with miliaria failed to respond.

Untoward Results.—In two cases, both of disseminate neurodermatitis (atopic eczema) dermatitis venenata was caused by the modified antihistaminic ointment. Application of the ointment to raw surfaces caused burning in some instances. Several patients with disseminate neurodermatitis reported a drying sensation after prolonged use of the ointment. Two cases of this group, with dry, lichenified skin, felt more comfortable by application of the control ointment than with the modified antihistaminic ointment.

SUMMARY AND CONCLUSIONS

1. A modified antihistaminic ointment (Calthenamine ® consisting of methapyrilene hydrochloride combined with calmitol liquid in a bland, water-miscible base) was investigated for the treatment of pruritus accompanying certain dermatological conditions. For control, the bland base of the same ointment was employed.
2. Excellent or satisfactory amelioration of pruritus was noted in most cases of urticaria from insect bites and other causes, localized neurodermatitis and dermatitis venenata. Fairly satisfactory relief of pruritus was noted in about half the cases of disseminate neurodermatitis and anogenital pruritus. Miliaria failed to respond. In two cases of disseminate neurodermatitis, the modified antihistaminic ointment increased irritation.

(Continued on Page 514)

PRECIPITIN REACTION IN THE DIAGNOSIS OF ALLERGIC PATIENTS

C. JIMENEZ DIAZ, E. ARJONA, J. M. ALES and J. M. SEGOVIA

Madrid, Spain

If the controversial but obvious relationship between the clinical phenomena of allergy and anaphylaxis is considered, it is no wonder that antibodies similar to those of anaphylaxis have been sought in the serum of patients with asthma, hay fever and other allergic diseases. The investigation of precipitins has been consistently negative until Cannon (cit. 1) and Cohen and Weller,² using Zozaya's method,¹⁸ carried out a careful investigation of these antibodies in the serum of sensitized patients. The method rests upon the increase of the micella by adsorption of the antigen on collodion particles thus making precipitation easier. Cannon, besides finding precipitins in the sera of sensitized animals, found them in four of seven patients sensitized to egg; Cohen and Weller found them at low concentrations of up to 1/640 in a patient sensitized to fish-glue. In non-treated patients sensitized to ragweed, the results were always negative while six treated pollinosis patients exhibited weak results in two and strong in four.

Considering that this reaction is essentially precipitinic and only differs from those obtained with the usual techniques by its pronounced sensitivity to collodion, this fact was deemed to be important since from a conceptual viewpoint it confirms the similar mechanism between anaphylaxis and allergic shock. Having become acquainted with these papers we performed some works to show how often and under what conditions the precipitin reactions appear with this technique. Our clinical and experimental results have been collected in a series of papers which we have already published;^{1,2,8,14} we shall now report them in a summarized form, laying stress on the practical and theoretical value which may be gained with this method of clinical examination in allergic disease.

To date, we have carried out the precipitin reactions in 2,400 cases grouped under different conditions in which allergic sensitization may be involved. One hundred and fifty-four normal subjects were used for control. Of the former cases, 755 belonged to asthmatic patients and in this report we shall only deal with them. A valuable experience has been gained from the painstaking studies carried out in these last four years which evidences the practical value—together with other methods—of precipitin studies in the determination of causative allergens. It is for this reason that a short report of the results have been set forth.

TECHNIQUE

The same technique described by Zozaya was used at first.¹⁸ Collodion was well purified by washing in distilled water for six to ten days, then

From the Medical Clinic and Institute for Scientific Research of the University of Madrid. Dr. C. Jimenez Diaz is an Honorary Fellow of the American College of Allergists.

washed in 96 per cent alcohol thrice, twice in absolute alcohol and lastly dried with calcium chloride. Once purified, 5 grams were dissolved in 20 grams of absolute alcohol and in 75 grams of anhydrous ether. This solution is poured off, filtered and precipitated with distilled water, then washed several times and dried between sheets of filter paper. When dry, it is dissolved in very pure acetone, the solution is rapidly shaken in the electric shaker and distilled water is slowly added meanwhile to form a whitish suspension which is further diluted till clots appear. Acetone is excluded by vacuum distillation, and the large particles of collodion are removed from the remaining suspension by centrifuging at 3,000 r.p.m. for two minutes. Centrifuging is performed twice, once for ten minutes and another for thirty minutes (a few crystals of sodium chloride are added beforehand), thus separating the second and third fractions of the collodion particles. The latter, i.e. the finest, are washed with saline and kept in the icebox till use is made of them. Adsorption was then carried out with the antigen and the reaction was performed following Zozaya's method.

But Goodner's⁷ procedure was soon made known to us, a simplified technique and therefore of greater use in practice. A series of comparative tests were performed with the same sera,² and it was noted that the latter technique was very exact. It was therefore put to current use with a few modifications. Antigen is poured into ten agglutination tests tubes (0.5 c.c. into each), diluted from 1/20 to 1/5120, and 0.1 c.c. of the patient's serum and 0.4 c.c. of the collodion suspension is added to each tube, prepared according to the technique of Zozaya. The concentration is the same as that of a 2,000 million germs per c.c. anti-typoid vaccine. The tubes are shaken, taken to the autoclave for one hour at 37° C. and then kept in the icebox till the next day when the results are taken down.

Experience has taught a few facts which are considered interesting as regards practice. In the first place, old or hemolized sera must never be used. The former may give rise to non-specific precipitation if not perfectly kept, and as for hemoglobin in hemolized sera, it may likewise determine false reactions. It is deemed convenient that the subject be fasting when the blood sample is taken and that female patients should not be menstruating at the time. Otherwise, precipitations of doubtful value may be exhibited in some instances.

It is essential for the antigens to have a 7.8 pH, and this may be obtained with a phosphate buffer. The protein content is also of interest although it may not be the only substance which precipitates. When positive sera with different concentrations of antigen are examined, it is seen that the degree of the reaction varies according to the protein concentration of the antigen. Thus antigens are used with a known protein nitrogen content by adjusting the concentration in such a manner that 1 c.c. contains 10 mg. of protein. The antigen is diluted when the reaction is performed: 0.1 c.c. to 10 c.c. of saline, i.e., 1 mg. of protein in 10 c.c.

RESULTS

1. Positive Reactions in Subjects with No Allergic Disease.—With the precipitin reaction, positive results are obtained in 40 to 48 per cent of the allergic patients under study. This percentage varies somewhat in the different disease groups, but as a rule they fall within the above figures. The precipitin reactions have been studied in 120 subjects with no allergic disease and several of the most common food antigens have been tested, the same in these as in the other patients. One or more positive reactions were only obtained in fourteen cases (11.6 per cent). No positive results were obtained in thirty-four normal subjects tested with the precipitin reaction for different common airborne fungi.

This small proportion of positive results in normal subjects is all the more surprising when compared to the positive results in sensitized patients. It is a point in favor of the specific value of the positive results since, otherwise, a greater number of false positive results should be obtained in normal subjects.

The positive results in normal subjects do not of necessity indicate that they are non-specific since it is known that some subjects possess a symptomless sensitization. This is known as a balanced allergic condition (Vaughan;¹⁶ Jimenez Diaz⁹). Passive transfer (Prausnitz-Küstner) may also elicit reagins in normal subjects (Tuft,¹⁵ Colmer and Rackeman¹¹). These facts only confirm the value of sensitization in many cases, to such a point that undeveloped sensitizations flare up when the patient contracts a condition which may be influenced by allergic shock, e.g., asthma or urticaria.

It may be gathered therefore that these reactions in normal subjects are rare and there is no reason for not considering them as specific, as though present in allergic patients.

2. Precipitin Reactions in Patients Afflicted with Different Types of Bronchial Asthma.—Our current experience involves 755 cases of asthma examined with this method. Of these, we have obtained one or several positive results in 307 cases to different antigens. Conversely, reactions were negative in 448 cases. The positive rate of 40.6 per cent contrasts with the 11.6 rate in non-allergic subjects.

Not all forms of asthma exhibit positive results at the same rate since, as we shall see presently, there are certain types of sensitization which never give a positive precipitin reaction, others only occasionally, and the remainder in which positive results are common.

(a) *Pollinosis.*—Thirty patients with pollinosis asthma have been investigated, using different pollen; in every instance, the cutaneous test and P-K.r. (Prausnitz-Küstner reaction) assured us of the sensitized condition. Our results have always been negative and it has therefore been inferred that no case of asthma by pollinosis is disclosed by precipitin reactions.

(2) *Asthma influenced by food.* We have grouped the cases in which food is responsible for the asthmatic condition into two types: in one group those cases of anaphylactic asthma, or with pronounced idiosyncrasy, in which the onset of the asthmatic attack and other numberless phenomena (cough, micturition, purpura, etcetera) is brought about by minute amounts of a foodstuff. It is the case of individuals sensitized to eggs, fish, etcetera, who mention the offensive food on being questioned. The other group is made up of cases which are more common, involving several foods and therefore more complex and not always brought to the patient's notice. It is the complex food asthma (Jimenez Diaz & Funk¹) or intrinsic asthma according to Rackenstuhl.² The difficulties encountered in practice to establish the different factors involved is well known by all. It is for this reason that elimination diets have been used, such as those of Rowe³ or the leukocytic test of Vaughan⁴ or pulse count as advocated by Coca.⁵ In our experience, only the elimination diet can furnish reliable data in some cases although, in many others, it is useless and, furthermore, it is a tedious and complicated method at times.

It is in this type of patient that interest lies in a diagnostic method which renders food influence objective since cutaneous reactions are negative and weak or multiple results are of little value. Passive transfer is almost always negative, and for this reason Coca⁶ has termed this type of allergy "familial non-reactive food-allergy" or idioblapsis. The fact is that it is precisely in this group that we have obtained the most interesting results with the precipitin reactions.

Of 328 cases of complex food asthma, 144 exhibited positive precipitins using ten antigens which are those used commonly as a starting point.

Positive results are distributed in the manner shown in Table I. The percentages refer to each food in particular, that is to say, to the number of times it has been positive. It must be remembered that many patients exhibited positive reactions to two or more foods.

TABLE I.—FREQUENCY OF POSITIVE RESULTS FOR EACH FOOD

Bread	27 times	18.7%	White fish	19 times	13.1%
Potato	19 times	13.1%	Blue fish	30 times	20.8%
Banana	12 times	8.3%	Meat	56 times	38.8%
Rice	12 times	8.3%	Milk	10 times	13.1%
Shell fish	23 times	15.9%	Eggs	36 times	25.0%

The practical value of these positive reactions is shown in the first place by the therapeutical results obtained by excluding harmful foods in the diet of the patient. In the group of asthmatic subjects we have noted favorable results in 60 per cent of positive cases. The results range from cases of cure to others of simple improvements of symptoms, according to the role played by food sensitization, alone or together with other factors, in the etiology of the asthmatic picture.

Although the arguments which uphold the specific value of precipitin reactions shall be discussed later on, we shall set forth a few examples to show our point.

Enr. Mor.—Male, thirty-six years (No. 823). Ever since the age of twenty-five, attacks of asthma which begin with stoppage of the nose, hydrorrhoea and sneezing. In the last years, they are more common and pronounced. On some days he is afflicted with four to six attacks during night and day time. Precipitin reaction elicits sensitization to potatoes, eggs, milk and white-fish. Elimination diets are prescribed on these data and the patient improves considerably. When he eats one of the above-mentioned foods, he is overcome by wheezing and oppressiveness in the chest fifteen minutes afterwards.

Mar. Rod.—Female, thirty-five years (No. 849). Complex asthma with major symptoms since childhood. All the findings are negative excepting the precipitin reaction which is positive for the kidney bean, blue vetch, bread, large bean and lentil. After a few months on an elimination diet, the patient reports that she is in excellent condition and that she has suffered no attacks.

These cases involve subjects with a non-pronounced type of food sensitization, who are seldom aware of the kind of harmful foods involved. We identify these conditions with Coca's non-reaginic allergy. On the other hand, in cases of marked anaphylactic sensitizations, the patient is usually aware of the harmful foods. Precipitins can be detected with the standard methods (named macroprecipitins by ourselves), while precipitins (microprecipitins) elicited with the collodion technique are negative.

J. Cab.—Male, twenty-two years (No. 2400). Eczema in face and head since childhood, which lasted for a long time. Eating potatoes, eggs and milk gave rise to highly pruriginous wheals and angioneurotic edema of the face and lips. Simultaneously, long-lasting catarrh and asthmatic bronchitis. At the age of thirteen, being in the country during harvest time, he had an attack of asthma which lasted for several hours. Since then, asthmatic crises from time to time which appear whenever he eats eggs or hake. Macroprecipitins are positive up to $\frac{1}{4}$ dilution of antigen for egg or hake. Precipitins with the collodion technique (microprecipitins) are negative with the same offending foods (antigen dilutions begin at 1/10).

TABLE II. POSITIVE FREQUENCY FOR EACH FUNGUS IN THE 58 POSITIVE CASES

Mucor	27 times=46.7%	Botrytis	10 times=17.2%
Alternaria	25 times=43.1%	Cladosporium	4 times= 6.8%
Aspergillus	25 times=39.6%	Sterigmatocystis	4 times= 5.1%
Penicillium	18 times=31.0%	Macrosporium	2 times= 3.4%
Stysanopsis	10 times=17.2%		

(c) *Asthma due to fungi.*—In the group of asthma due to sensitiveness to air-borne fungi, our present experience involves 160 cases studied with the precipitin reaction. At first, we only performed precipitation investigation in individuals who exhibited positive intracutaneous reactions to one or several of the tested fungi. Thus, in the first series of ten patients with clear sensitivity in the cutaneous tests, three were found with positive precipitin reactions to the very same fungi (*Alternaria*, *Aspergillus*, *Penicillium*) which had given rise to positive cutaneous reactions. More recently we have also tested the precipitin technique in cases of asthma which, on account of the clinical characteristics (connection with seacoast climate, time of onset, et cetera) seemingly involved fungi. Nevertheless, cutaneous reactions were negative. Thus do we find that of 160 total cases studied, fifty-eight had precipitins in the plasma involving one or several proven fungi (36.2 per cent positive).

Positive frequency for each fungus is shown in Table II in which percentages are reckoned in the same way as for the foods.

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It is worth while to compare the behavior of positive precipitin reactions with the results of cutaneous tests, as shown in Table III.

TABLE III. COMPARISON BETWEEN POSITIVE PRECIPITIN REACTIONS AND THE RESULTS OF THE CUTANEOUS TESTS

	Pos. Precip. Pos. Intracut.	Pos. Precip. Neg. Intracut.	Total
Mucor	10	17	27
Alternaria	7	18	25
Aspergillus	7	16	23
Penicillium	5	13	18
Stysanopsis	4	6	10
Botrytis	4	6	10
Cladosporium	2	2	4
Sterigmatocystitis	1	2	3
Macrosporium	0	2	2

At first, agreement between both tests was a source of great worry to us since it was considered that the existence of precipitins in the patient's serum confirmed the existence of reagins in the skin; we admitted the possibility that it might be the same antibody evidenced by different routes. Later on, wide clinical and experimental experience reported in different publications^{1,2,8,14} has convinced us that the precipitin (microprecipitin) and reagin are two different antibodies which may or may not coexist in the same subject. It is to be noted that, in the above Table III cases exhibiting agreement between both tests are fewer than those exhibiting disagreement, i.e., in which a positive precipitin reaction is noted with negative cutaneous reactions. This fact is very significant since objective data—the precipitins—are elicited in many cases of asthma suspected of being produced by sensitivity to fungi and yet showing negative results with the classical tests. This contention is true to such a point that in our department of allergy, wherever a patient is examined with a clear history involving a climatic factor and showing a positive precipitin reaction to one or several fungi although the cutaneous reactions are negative, we prescribe a desensitizing treatment with extracts of the offending fungi. We can thus treat a great number of patients with specific means who would otherwise be treated with non-specific measures. The therapeutical results gained in these instances support this procedure.

The following cases are given as demonstrative examples of the facts contended above:

May. Berg.—Female, eight years (No. 2430). Since the age of three, asthmatic attacks with great frequency which disappear whenever she leaves the seacoast town where she is living. Among the many treatments prescribed, the last has been penicillin aerosol. On inhaling the drug for the first time, she is overcome by an acute shock involving spasm of the glottis, apnea, cyanosis, et cetera, reduced after a time with injections of adrenalin. The cutaneous reactions and P-K.r. are positive to *Penicillium* and penicillin. Precipitin test is strongly positive for penicillin and still more for *Penicillium*.

In this case, the cutaneous reactions and precipitins were positive and the latter confirmed the value of the first. The following case is even more interesting since only the precipitins were positive:

Ad. Nog.—Male, nineteen years (No 3303). Six months ago, bronchitis with large amounts of sputum; fever ranging from 38° to 39° C. Dyspnea and coughing more recently, particularly at night-time. Dampness troubles him, giving rise to fatigue and hoarseness. Cutaneous reactions are negative to different antigens, among them *Mucor*, *Alternaria*, *Cladosporium* and *Aspergillus*. Nevertheless, precipitins are strongly positive with aspergillus. The patient is treated with three concentrations of *Aspergillus* extract. He is once again examined six months later and found to be in excellent condition, without fatigue or cough and having a good appetite.

(d) *Asthma produced by cereal dust and parasitic fungi.*—In asthmatic patients sensitized to dried vegetable or cereal dust and to parasitic fungi of the latter (tilletia, ustilago), it is common to elicit positive cutaneous reactions and passive transfer of sensitiveness with P-K.r. In many cases, determination of precipitins with the collodion technique shows positive results with the same antigens, agreeing therefore with the cutaneous tests. But in other cases, in which the clinical history evidences sensitiveness to cereal dust or to parasitic fungi, the cutaneous tests are negative. In these instances, the same as in asthma due to air-borne fungi, the precipitin reaction is a valuable aid in the etiologic diagnosis of the sensitization.

We have studied 182 patients with asthma who, on being questioned, gave details which pointed to sensitization by dried vegetable or cereal dust, owing to the fact that onset befalls when in contact with granary dust, straw, et cetera. The presence of precipitins was disclosed in eighty-four cases with suspected antigens (46.1 per cent), coincidental or not with positive cutaneous tests.

The number of times that each of the tested antigens was positive and the behaviour of cutaneous reactions is shown in Table IV.

TABLE IV. ASTHMA DUE TO DRIED VEGETABLES, CEREALS AND PARASITIC FUNGI: FREQUENCY OF POSITIVE PRECIPITINS AND COMPARISON WITH CUTANEOUS TESTS

Antigen	No. Times Tested	No. Times Pos. Reaction	Per cent Pos. Reaction	No. Times Pos. Intracut.	Per cent Pos. Intracut.
Tilletia	86	33	38.3	14	19
Ustilago	86	23	26.7	8	15
Cereal dust	90	27	30.0	11	16
Wheat	62	12	19.3	4	8
Barley	50	10	20.0	4	6
Rye	48	10	20.8	5	5
Oats	22	5	22.7	3	2
Tare dust	27	8	29.6	7	1
Indian bean dust	3	1		1	0
E. cervilia dust	1	1		1	0
Blue vetch dust	2	1		1	0

With this series of patients, something similar to what occurs in the group of asthma due to fungi is found to exist; the rate of negative cutaneous tests and positive precipitin reactions is greater than the number of times both tests are found to agree. It is once more stressed that the reason for this lies in the different existing antibodies which may or may not be found simultaneously in a patient. In many cases, both tests comple-

ment each other since the cutaneous reaction showed that one antigen was the sensitizing agent while the precipitin test elicited another. Hence, patients have been successfully treated who otherwise would have entailed failure. It can be affirmed on studying our statistics that the detection of precipitins is a better guide to treatment than positive cutaneous reactions since it is common for the latter to be negative with no evident passive transfer (P-K.r.). The following examples stress our point:

Gab. Gag.—Female, forty-five years (No. 2882). Lives in the country. Four months ago, dyspnea, wheezing and oppressiveness in chest, frequently recurring. Smoke and home and granary dust trouble her. When she came to Madrid, she became symptomless. Cutaneous tests with airborne fungi, parasitic fungi, home and cereal dust were negative. Precipitins positive with cereal dust. She is treated with cereal extract becoming symptom-free.

Hip. Ru.—Male, fifty-one years (No. 3190). Tends to be afflicted with catarrh. Twelve years ago, during one of these bouts, pronounced fatigue which lasted for four days. From then on and coincident with catarrh, dyspnea and wheezing lasting for several days. Occasionally, attacks with underlying asthma. He is greatly troubled by smoke, and cereal, wheat, barley and rye dust. Precipitins positive on wheat and rye test. Cutaneous tests negative for all the antigens tested. Shows striking improvement on wheat and rye extract treatment.

Pet. Zorr.—Female, forty-seven years (No. 3208). At the age of twenty-six, pronounced catarrh involving fatigue and bouts of dyspnea at night. Since then, has a common tendency to catarrhs and fatigue. When breathing air carrying granary, straw or threshing floor dust, he is overcome by pronounced fatigue and wheezing. Serum tests elicit strongly positive precipitins for tilletia, rye and oats. Conversely, cutaneous reactions are all negative. Shows great improvement on treatment with extracts of these offending antigens.

Precipitins occasionally elicit the existence of reagins when cutaneous reactions are negative (possibly due to a defective technique or to a weak antigenic power of the extract) or when values are non-specific.

Sant. Tom.—Female, thirty-four years (No. 2820). Nine years ago, acute catarrh with wheezing, dyspnea and thoracic oppressiveness involving hydrorrhoea of the nose and photophobia. Remained in good health for three years and then exhibited attacks of asthma. Since then, coryza and fatigue which increases when moving wheat to the granary. Cannot feed the cattle because he is overcome by breathlessness. Precipitins positive for ustilago and cereal dust. Cutaneous reactions are negative with these antigens. Nevertheless, when results of precipitin reactions were known, passive transfer (P-K.r.) was performed and clear positive results were obtained for ustilago and cereal dust.

Alej. Par.—Female, fifty-eight years (No. 3279). Catarrh every winter with fatigue and wheezing. In June and July her condition worsens. Cereal dust makes sneeze and brings on fatigue. Cutaneous reactions: tilletia, negative; ustilago, + + +. Precipitins: tilletia, + ++ + +; ustilago, negative. P-K.r.: tilletia, + + +; ustilago, negative.

(c) *Other types of asthma.*—Different cases of asthma due to varying agents have been collected in this group. The precipitin technique following our procedure was of great diagnostic value in some instances.

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Animal fluff (epithelial scales) and other skin products: Nine cases have been studied in which sensitization by fluff of different animals was suspected. Cutaneous reactions were positive for all these antigens but precipitins were only positive in five cases.

Eduv. Rui.—Female, forty-four years (No. 1385). From the age of twenty, asthmatic attacks, mainly at night. They only supervene in her native village and her condition improves when traveling. She cannot go into a stable since this act brings on pronounced dyspnea. Precipitins positive for mule fluff. Intracutaneous and P-K. reactions positive. Irritation test (nasal reaction) is likewise positive.

The following is an unusual case of sensitiveness to cat hair. Cutaneous and precipitin reactions were clearly positive.

Mar. Fra.—Female, eighteen years (No. 1282). Attacks of asthma since a child. During the intervals between attacks, fatigue of varying degree. Numberless tests (cutaneous) with different antigens were negative. It was discovered that two cats slept in her bed. Cat hair extract was used to investigate precipitins in the patient's serum. Results were highly positive as also the cutaneous reactions which involved pronounced local and general phenomena. The cats were removed from her home and her condition improved leaving her symptomless.

Precipitins occurred in four cases of twelve involving asthma due to woolen materials or feathers. One of these is particularly interesting since sensitiveness to the wool of the mattress was suspected but cutaneous tests were negative.

Merc. Gab.—Female, twenty-nine years (No. 2481). Since childhood, attacks of asthma which have increased in number and intensity. Onset usually supervenes in bed at night. If she goes to bed during daytime, she is also afflicted by asthmatic attacks. The mattress contains woolen material. Cold and dampness worsen her condition. Cutaneous reactions using wool from her mattress are negative. Precipitin with the same antigen are positive. Treatment is prescribed with three strengths of wool extract. Four months latter she writes, ". . . I have followed treatment according to your instructions and I am now free from fatigue. I occasionally feel slight disturbances and cough a bit at night. . . ."

In nine cases, precipitins for dust from the home of the asthmatic patient were investigated. Results were positive in three cases; likewise the cutaneous tests.

In twelve cases of asthma due to insects, we have never obtained precipitins in those due to cimex, whereas cutaneous reactions and P-K.r. were clearly positive. There were ten cases of cimex sensitization. The two remaining cases were due to the wheat weevil ("Calandra granarius" or "sitophilus granarius") and in these, precipitins were positive. The first case has already been published (Jimenez Diaz, Lahoz and Canto).¹⁰

Within the group of occupational asthmas, we have collected twelve cases. Precipitins were studied. Five patients were bakers, four millers and the other three handled different kinds of flour. Positive precipitins were found in six cases: three for common flour, two for flour containing parasites, and one for mill dust.

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Man. Can.—Male, forty-five years (No. 3407). Baker. For many years he tends to be afflicted with catarrh, wheezing and oppression in the chest. In the last twelve months, attacks with underlying asthma, particularly during sleep (he sleeps during the day) and when in the bakery. Flour dust troubles him greatly. He feels much better whenever he leaves work. Cutaneous reactions are negative for many antigens including several kinds of flour. Precipitins are clearly positive for parasitic flour (wheat).

This and many other cases prove clearly that a correct diagnosis of the offending and sensitizing antigen would never have been established if the precipitin reaction had not been used. It exemplifies the value of this technique, particularly where cutaneous tests remain negative.

In Table V, all the cases of asthma mentioned in the last group have been collected.

TABLE V

	Total	Pos. Precip.	Nega. Precip.	Pos. Pos. Intracut.	Precip. Neg. Intracut.
Animal fluff.....	9	5	4	5	0
Cat hair.....	1	1	0	1	0
Wool and feathers.....	12	4	8	2	2
Dust from the patient's home.....	9	3	6	1	2
Insects: Cimex.....	10	0	10	0	0
Insects: Calandra.....	2	2	0	2	0
Occupational asthma.....	12	6	6	2	4
	55	21	34	13	8

It can be affirmed, on glossing over the foregoing, that the precipitin reaction is useless in pollinosis asthma, since sensitization in this type of allergy is purely reaginic.

In non-anaphylactic food asthma, in which it is considered that cutaneous tests are of no value and other tests are unreliable (Coca's and Vaughan's tests), precipitin determination is held to be the best for diagnosis (microprecipitin sensitization).^{1,8,14}

The following are included in both groups: climatic asthma, asthma due to dried vegetable dust, to cereal, house, animal fluff, insect dusts (excluding cimex) et cetera. In these, precipitins furnish, in some cases, confirmatory proof of sensitization elicited by cutaneous tests and, in other cases, they complement the results of the latter. Lastly, in numerous cases, they elicit sensitizations which would otherwise have gone unperceived.

TABLE VI. SUMMARY OF CASES OF ASTHMA STUDIED WITH THE PRECIPITIN TECHNIQUE

Group	Number	Pos. Precip.	Per Cent	Neg. Precip.	Pos. Precip. Pos. Intracut.	Pos. Precip. Neg. Intracut.
Pollinosis asthma.....	30	0	= 0	30	—	—
Food asthma.....	328	144	= 43.9	184	—	—
Fungi asthma.....	160	58	= 36.2	102	30	84
Cereal asthma, etc.....	182	84	= 46.1	98	59	77
Several others.....	55	21	= 38.1	34	13	8
Total.....	755	307	= 40.6	448	102	169

DISCUSSION

It is deemed that the data put forth in this paper show the great practical

interest attached to the precipitin reactions, as performed by ourselves, in routine and systematic examination of asthmatic patients.

Doubt might be expressed as to the specific value of these reactions. The following arguments are set forth as a proof of clinical value and specific character of this method:

1. The reactions obtained in many of these patients have been repeatedly carried out. Where the patients have not been treated meanwhile, the results have been uniform. It is contended that if the reactions were not specific, the results would vary from case to case.

2. The results of the tests and the case history have always been coincidental. Positive reactions have never been obtained with cereal extract in patients who have never come into contact with them. The same hold for home dust, fungi, et cetera. However, on testing food, fourteen positive tests have been obtained in 120 subjects who were not asthmatic and who were not afflicted with any other allergic condition. However, this fact does not discredit the method since it involves symptomless sensitization.

3. In numerous cases in which precipitin reactions have been positive, stimulation tests have been confirmatory.

4. The elimination of the offending antigen has influenced the course of the condition. When the precipitin reaction is only positive for one antigen in a patient, e.g., cases of asthma due to dust, suppression of contact has done away with the attacks.

5. Another point in favor of the specific value of the precipitins evidenced by collodion technique is the experimental and elective production in laboratory animals; reports have been published elsewhere by ourselves.^{1,8}

The specific value of this test is deemed to be evident. The reason for sensitiveness with positive precipitin reaction and others with negative results remains to be discussed. It is believed that the same occurs in this instance as with cutaneous reactions and passive transfer. There are sensitized patients who exhibit positive reactions with the latter while others exhibit negative results. When pollen causes asthma, cutaneous reactions and passive transfer tests are commonly positive but, as mentioned beforehand, precipitins are never noted. Conversely, when food sensitiveness is considered—excepting marked idiosyncrasy in cases of complex, multiple sensitization—cutaneous reaction and P-K.r. are negative since this type of sensitiveness involves non-reaginic components. It is obvious that the precipitin antibody evidenced by this technique differs from the reagin and may or may not be coincidental. Hence, reaginic, precipitinic or mixed sensitiveness is found. It probably depends on the nature of the antigen, route of entry and degree of contact. The experimental studies performed^{1,8,14} confirm these viewpoints.

It has been deemed essential to find out whether the antibody which causes these reactions is the precipitin obtained experimentally in sensitized animals. A series of studies have shown that such is not the case. In animals with positive precipitins according to the classical technique, which

can be termed macrotechnique, it is found that the diluted serum will not exhibit precipitin reactions performed with the collodion technique, which may be termed microtechnique. The same holds true for appropriate sera of patients. For example, no positive reactions are obtained with collodion when the serum of a patient with precipitins (macrotechnique) for strawberries is diluted. Thus, it is believed that the causative antibody in these reactions is not the anaphylactic precipitin nor is it connected to the reagin.

Investigations have also been carried out to see if the blocking-antibody of Cooke, Bernard, Heball and Stull⁵ might be involved. For this reason, microprecipitins in the sera of patients under treatment for pollinosis and blocking-antibody titres have been studied at the same time. Results were negative: blocking antibodies rose steadily but the microprecipitin reaction was consistently negative.

In short, we are dealing with a little-known antibody which we have termed microprecipitin for the time being, heat-stable,¹⁴ the offending antigen for a certain time.^{1,8,14} It is definitely not the common precipitin (macroprecipitin), reagin or blocking-antibody. There is evidently a macroprecipitinic or anaphylactoid sensitization, as evidenced by experimental anaphylaxis or major idiosyncrasy in man, generally caused by a certain food. A reaginic sensitization undoubtedly exists, best exemplified by pollinosis, with reagins and without microprecipitins. Lastly, we have sensitizations (many cases of multiple food sensitiveness, dusts, fungi, parasites, et cetera) with microprecipitins which may or may not associate with reagins.

SUMMARY

The authors describe the technique for the precipitin reaction, based upon the adsorption of the antigen on collodion. It has been used to study the existence of specific antibodies in normal subjects and in asthmatic patients where etiology involves different factors. This antibody, termed microprecipitin by the authors, bears no connection to the precipitin shown with the classical technique; nor to the reagin or blocking-antibody.

In the serum of patients with certain types of allergy, a precipitin of the anaphylactic type can be demonstrated, in others, the reagin and, in others still, the microprecipitin. Thus the authors admit three types of allergy: macroprecipitinic, reaginic and microprecipitinic. As a rule, in major sensitizations (idiosyncrasy or anaphylaxis due to food), macroprecipitins and reagins are demonstrated. Only reagins are found in pollinosis and in complex, non-reaginic, food sensitization, in which neither the cutaneous reaction nor the passive transfer are positive, microprecipitins are found. In asthmatic patients sensitized to different kinds of dust, in climatic asthma and in those due to danders and insects, both antibodies—microprecipitin and reagin—or only one of them can be found. Data on

(Continued on Page 529)

FOOD ALLERGY

A General Discussion of Twenty-five Years of Experience

I. S. KAHN, M.D.

San Antonio, Texas

THIS discussion is based on some twenty-five years of a practice limited to allergic diseases, which naturally would include the study of many, probably several hundred, cases in which food allergy played the sole or a significant role.

The purpose of this discussion is to clarify some practical points that are of importance in reducing failures in the management of these cases. These points to be mentioned are based on our own difficulties and are based also on cases that have actually been only too frequently overlooked by internists and allergists who had previously handled many of these cases. The overlooking of these points brings unjustified discredit to methods which are highly successful if properly applied.

The first practical point is that while conditions such as infantile eczema, adult atopic dermatitis, and allergic cephalgias can be perhaps usually ascribed to food sensitivity, such is not by any means invariably the case. An appreciable number of cases of eczemas especially fall into the category of contact dermatitis in which the food element plays only a minor or absolutely no part whatsoever. Even chronic urticaria is not invariably due to food allergy. We have in our records a few such instances due to bedding and the usual house dust factors. The pollen element enters into a small number of urticaria cases, proven by the cessation of cutaneous lesions on unrestricted diet on removal to an atmospheric pollen free environment. Many cases of migraine or allergic headaches have been reported by others due purely to antigens of the house dust type. Nocturnal or early morning symptomatology with nasal blockage definitely suggests a possible non-dietetic etiology.

Thus the failure to secure positive skin tests to foods in all instances where expected, should lead not to unfavorable criticisms of the tests, but to consideration of non-dietary factors. This statement would also include naturally those cases where the withdrawal of secured positive skin test foods has made no change in the clinical picture. These positive reactions may represent long forgotten past sensitivities. They also could indicate current clinical sensitivity only with rare excessive ingestion, or act under certain conditions, as factors in the production of allergic symptoms entirely foreign to those presented at the time being. However, they may be of decided importance taken in conjunction with the main non-dietary factors, or the main non-reacting foods. Their routine withdrawal if they are not too numerous does no harm, even if only of occasional necessity. Consequently, in the above mentioned conditions the finding of negative skin tests to foods may be entirely correct.

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Now a few more words regarding skin tests. In spite of many apparently incongruous findings, I feel that skin testing is extremely valuable and should be a routine procedure. I find the dermal tests seldom of diagnostic value. However, they should be done in considerable number for two reasons: first as a preliminary index of safety for subsequent intradermal work, and secondly, to exclude the possibility of some unusual unsuspected antigen, occasionally of a high degree of sensitivity, such as flaxseed or cottonseed.

Some consideration here should be given to the not uncommon failure to secure the expected definite whealing intradermal tests to food antigens later proven of clinical significance.

First comes the masking of each reaction by antihistaminic drugs, a matter of increasing importance with the prevailing widespread self and ordered administration of such drugs. Secondly comes the fact that in many such ingestion cases due to commonly used foods such as milk and the cereals, the actual degree of sensitivity is low, beyond the powers of the skin tests to produce typical diagnostic wheals, giving as a test result merely small papules. A child taking two quarts of milk a day with only chronic indigestion and general ill being, must possess actually only a relatively low degree of sensitivity. Were such sensitivity of high degree calling for a positive scratch test or usual undoubted diagnostic intradermal wheal, the clinical ingestion response would be immediate vomiting or symptoms of acute severity.

In these instances of low degree sensitivity, the intradermally secured small papule or a delayed tuberculin type reaction may thus be diagnostically correct.

Also, certain testing materials such as strawberries frequently give negative skin tests in the face of undoubted clinical sensitivity.

Another complicating factor is that false positives are occasionally secured in deteriorated testing material, probably from some decomposing histaminic element.

Still another disconcerting factor consists of the numerous false positives seen in the urticarial hypersensitive skin, making specific diagnosis by skin tests impossible. Passive transfer here may be resorted to but is rarely necessary, as such extreme skin hypersensitivity will usually disappear after a few weeks or less employment of a diet later to be suggested.

In routine testing in food allergy cases where there is no cutaneous irritability, one or several positives, usually of a minor degree, are encountered fairly frequently. These may or may not be of clinical significance. However, these minor positives should be closely regarded during the active symptom period, in spite of the fact that they may be only temporary in character and of no importance following symptom clearing. However, one reason for failure in this work is the assigning of primary importance to these minor accessory food factors with weak positive

skin tests, and the exclusion from consideration of the actual prime specific non-dietetic factors. Food positives in bronchial asthma fall into this category. We only occasionally find any dietetic item of clinical importance in the production of asthma.

Where specific food allergy has been correctly diagnosed and where the appropriate corrective dietary measures have been instituted, another cause of failure is the non-recognition of the fact that in old chronic cases following initial betterment a period of time, possibly of several weeks, may be required before complete elimination of the pathological process occurs; especially is this true of old chronic cereal urticaria or eczema cases. This occasionally leads to the partial or total abandonment of the absolutely needed prolonged strict cereal abstention, and the unwarranted assumption of psychomatic influences, or of the importance of the other food positives found on the initial or at various later test sittings. This state of affairs has also been noticed by Albert H. Rowe of Oakland, California.²

Another common cause of failure in food allergy is the non-recognition of the deleterious effects of drugs (other than the antihistamines), especially those of a purgative laxative or analgesic character, also opiates and salicylate derivatives such as aspirin. Constipation should be corrected where necessary by low enemas, not by drugs. Occasionally a few drops of dilute hydrochloric acid daily will assist in reducing flatulence where present. On the whole, it is safe to recommend complete elimination of drugs. The antihistaminic drugs, of course, do not fall into this category. They could and should be used to the degree needed for comfort, especially in skin cases, to obviate delayed resolution due to non-specific irritation from itching and scratching.

Another extremely important point now presents itself. It is undoubtedly true that a single cereal sensitivity at times exists. However, in my experience, this is far from being the usual state of affairs, and the non-recognition of wheat sensitivity in many instances as a complete cereal group sensitivity is an extremely frequent cause of failure in wheat and cereal cases. For consistent results, I have not been able to substitute any one cereal for another, and hence all are omitted, also of course, all cereal products (bread, biscuit, crackers, hot cakes, waffles, spaghetti, flour thickened soups and gravies). Malted drinks, corn, rice and rye products are included in this prohibited category. Our experience shows that many failures are due to the use of breads and wafers of these substitute cereal products in wheat cases. The rice content explains the many failures of the long used diagnostic semi-starvation diet of lamb, rice and canned pears. Well-done crisp melba toast made from plain, not whole wheat flour, oven heated for twenty-five to thirty minutes, makes an excellent cheap practical bread substitute. In twenty-five years we have encountered only a single cereal case that could not tolerate melba toast

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so prepared. Hence we find totally unnecessary the more expensive and more difficult to prepare, bean and potato flour substitutes. The Mexican corn tortilla crisply toasted makes another excellent bread substitute.

NAME _____	DATE	From	To	
BREAKFAST	LUNCHEON	DINNER	EXTRAS	SYMPTOMS
Sunday				
Monday				
Tuesday				
Wednesday				
Thursday				
Friday				
Saturday				

Fig. 1

Another rarer cause of failure exists. I am referring to the patients' other allergic conditions such as vasomotor rhinitis or pollenosis. Their correction by appropriate measures may be needed in some instances to assist in restoring the allergy balance necessary for the clearing of an obstinate food allergy affecting primarily the skin or gastrointestinal tract.

Local dietary habits are possibly of some importance in the relative frequency of individual antigenic food items. For instance, in southwest Texas, citrus fruits are of importance and we seldom see fish or potato cases.

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An understanding of these points is necessary before any degree of consistently good results can be expected from any form of dietary control of food allergy.

Specific diagnosis in food allergy can be determined by various methods:

1. By overfeeding of suspected foods.
2. By skin tests.
3. By dietary restrictions and subsequent resumption of individual food items.

The first method of overfeeding suspected food elements to intentionally increase symptoms has not attracted our office, and we have had very little experience with it. It will occasionally differentiate between contact and dietary eczematous conditions.

Some form of dietary diary is essential in this work. One with a column giving the hour of symptom onset is especially valuable. A careful scrutiny of this dietary diary and repeated testing of the possible incriminating deleterious factors it suggests, will usually sooner or later reveal in primary milk or cereal cases, secondary unsuspected sensitivity or minor sensitivities that are delaying clearing (Fig. 1).

The appended diet that follows, reported by us in 1940,¹ has proven its value by its routine use in our office for many years, a diet which has cleared a high percentage of old chronic cases within a few weeks, and even, in many instances, within a few days before the completion of food testing, which in our office is routinely spread out to several, not necessarily daily, sittings. This is due to the fact that a very high percentage of chronic food allergy is due to milk and the cereals which the diet takes care of. This diet gives these patients a practical diet of some variety, comparatively cheap, easily followed, and with the advantage of advising definitely what to eat as well as what to avoid. Of course, it is only a basic diet and will not uncover fruit, vegetable, or the more unusual sensitivities. These should be picked up by repeated testing and studying of the dietary diary.

SUGGESTED BASIC DIET FOR FOOD ALLERGY CASES

Breakfast.—Citrus fruit not more than once weekly. Other mornings, apples peeled or cooked, stewed prunes, grapes or grape juice. Crisp bacon, well cooked eggs, coffee or tea.

Dinner and Supper.—All meats, well cooked, except pork. All fowl. All white meat, scale fish.

All cooked vegetables (Watch tomato). Lettuce or cooked vegetable salads.

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Barred: Milk (as a beverage) nuts, chocolate, shell fish, berries, honey, melons, Coca Cola and all soda fountain drinks, and condiments except salt. Wheat and all cereal products except melba toast. This prohibition includes bread, biscuit, crackers, macaroni, spaghetti, cakes, flour-thickened gravies or soups, beer and in fact all malted drinks. Melba toast crumbs makes a good batter material. Tapioca, sago, and arrowroot where available may make good cereal substitutes. A small amount of accompanying canned milk is not forbidden. Potato flour can usually be substituted for thickening soups or gravies. Bread made from it we have not found practical. At least initially, total abstention from alcohol is preferable. If this is impossible to secure, the Mexican tequila or brandies derived from fruits make fairly good substitutes for grain derived alcoholic beverages.

In acute cases, or where dietary restrictions are to be of limited time duration, raw foods of every character are omitted. In this connection, in acute urticaria our own experience shows the common practice of an initial laxative or purgative apparently more harmful than beneficial.

Production of symptoms by ingestion of incompatible foods on an empty stomach is of course a requisite from a scientific proof point of view. Practically, it is not a necessary routine procedure. Patients will often through inadvertent, unavoidable, or intentional ingestion furnish such proof even where most of the time the food is not taken on an empty stomach.

However, as a matter of fact, no matter how desirable it may be from a confirmatory scientific point of view, it is not always possible to secure such confirmation of correctly diagnosed offending foods by dietary resumption on an empty stomach. Patients will not always consent. Also, even if instituted, the procedure is not invariably successful for the reason that it is not always possible to reproduce all the conditions specific and non-specific, which initiate the symptomatology. This is especially true if the sensitivities are multiple.

Patients are advised in advance of the weight loss that ordinarily follows any extended use of this basic diet. However, there is no loss of strength, and occupational activities ordinarily need not be restricted. Fattening foods can be added later, as shown innocuous by tests and clinical trial.

Neither our office nor our patients like permanent abstention from comparatively essential foods such as milk, eggs, or the cereals. With milk cases, except in very young children, we have no difficulties. We encounter very few adult cases desirous of its resumption. The various milk substitutes needed in pediatric practice are beyond the province of this discussion. However, canned milk will frequently be found innocuous in definite raw milk-sensitive cases, making a good cheap substitute. Cur-

ously enough, we see very few egg cases.' Practically all of our egg cases have no difficulty with hard cooked eggs. In the rare cases of extreme egg sensitivity, of course, meticulous total abstention is required.

With our cereal cases what our patients miss most is bread. Ordinarily, the sensitivity of wheat cases is not of extreme degree. By starting with an eighth of a slice of plain white bread and by long continued daily use, and slow increases over a period of weeks or months, we are able either to produce a certain amount of hyposensitization or to establish or discover a tolerance permitting a fairly satisfactory usage. We find this more practical than the flour-water method.

The acute cases of food allergy are usually self-limited and seldom offer any difficulties in specific diagnoses or handling. Testing is seldom called for.

The subacute and chronic cases present an entirely different problem of vastly greater difficulty. A simple practical basic initial diet for the control of these cases is presented. However, no conclusions should be drawn as to the value or nonvalue of this or any other dietary regime for the control of food allergy without a full understanding and consideration of the introductory factors mentioned at some length.

1708 Nix Professional Building

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MODIFIED ANTIHISTAMINIC OINTMENT

(Continued from Page 495)

3. None of the patients obtained relief of pruritus from the control ointment except two cases of disseminate neurodermatitis.
4. Although the investigation was essentially directed at a determination of the effect of the modified antihistaminic ointment in the control of pruritus, it was noted that in many of the successful cases, an improvement in the appearance of the lesions took place. The mechanism may have been one wherein the combination of histamine and tissue cells was prevented, or one wherein with the amelioration of pruritus (reducing the need for scratching) the lesions improved.

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EXPERIMENTAL AND CLINICAL EFFICACY OF TRIMETON AND CHLOR-TRIMETON MALEATE

S. MARGOLIN, Ph.D., and R. TISLOW, M.D.
Bloomfield, New Jersey

THE discovery by French scientists (Bovet, Staub, Halpern and Fourneau) that certain derivatives of ethylenediamine and ethanolamine are antagonists of histamine provided the impetus for extensive research resulting in the synthesis of many chemically related antihistaminic agents. Investigations in the laboratories of Schering Corporation have shown that an entirely new class of compounds, the propylamines, exhibits outstanding antihistaminic activity. Fortunately, these compounds are relatively nontoxic; and, when these laboratory findings were confirmed in the clinic, two new antihistamines, prophenpyridamine (Trimeton) and chlorprophenpyridamine maleate (Chlor-Trimeton Maleate) were introduced.^{7,17,18}

The antihistaminic activity of drugs can be evaluated by observing the inhibition of the pharmacodynamic effects of histamine. Among various *in vitro* and *in vivo* methods for the assay of antihistaminic activity, the most reliable and widely employed one is an *in vivo* test which measures the degree of protection of guinea pigs treated with antihistamines and challenged with lethal amounts of histamine (Halpern,⁵ LaBelle and Tislow,⁷ Loew⁹).

Guinea pigs are very sensitive to histamine. After administration of lethal doses of histamine, they exhibit signs of respiratory distress within a few minutes; convulsions and death occur. The mechanism involved is a muscular spasm of the bronchioles, which results in asphyxiation. However, guinea pigs which have received a sufficiently large oral or parenteral dose of an antihistamine prior to a lethal dose of histamine are protected from the bronchial spasm. The size of the dose of an antihistamine necessary to provide this protection is a measure of its antihistaminic activity.

At least three graded doses of the various antihistamines were administered orally to guinea pigs. Exactly one hour later each animal was challenged intravenously with a lethal dose of histamine dihydrochloride (1.1 mg/Kg of body weight). The number of protected animals was recorded, and the median protective dose (PD_{50}) with confidence limits was calculated by the method of Litchfield and Wilcoxon.⁸

In the acute toxicity determinations, several graded doses of the antihistamines were given orally to guinea pigs. The mortality was recorded for five days after feeding the drug. The median lethal dose (LD_{50}) and confidence limits were then calculated.

From the Schering Corporation, Bloomfield, New Jersey.
JULY-AUGUST, 1950

TRIMETON—MARGOLIN AND TISLOW

TABLE I. ORAL ACTIVITY AND TOXICITY OF SEVERAL ANTIHISTAMINES
IN GUINEA PIGS

Compound	Median Protective Dose		Relative Potency	Median Lethal Dose		Therapeutic Index LD50 PD50	Relative Safety
	PD50	Confidence Limits*		LD50	Confidence Limits*		
Chlor-Trimeton (chlorpropenpyridamine maleate)	mg/Kg	mg/Kg		mg/Kg	mg/Kg		
Trimeton (prophenpyridamine)	0.14	0.11 to 0.17	100.0	210	175 to 250	1500	100.0
Neo-Antergan (pyranisamine maleate)	1.5	1.1 to 2.0	9.3	270	218 to 321	180	12.0
Histadyl (thienylpyramine—HCl)	2.5	1.6 to 3.8	5.6	290	221 to 380	116	7.7
Benadryl (diphenhydramine—HCl)	4.0	1.8 to 8.8	3.5	460	336 to 632	115	7.7
Thephorin (phenindamine)	4.0	3.5 to 4.5	3.5	280	200 to 390	70	4.7
Pyribenzamine (tripelennamine—HCl)	3.2	2.7 to 3.9	4.4	185	124 to 276	58	3.9
Neohetramine (thonzylamine—HCl)	3.2	2.6 to 3.9	4.4	150	110 to 200	47	3.1
Antistine (phenazoline—HCl)	14.5	10.4 to 20.3	1.0	370	283 to 485	26	1.7
	36.0	25.7 to 50.4	0.4	440	306 to 633	12	0.8

*P=0.05

DISCUSSION

Statements have been made in a recent publication by Dreyer³ on the comparative properties of certain antihistaminic agents, although no quantitative data were presented to substantiate such statements. The comments based on certain *in vitro* procedures performed on guinea pig ileum, guinea pig uterus, isolated frog heart and isolated guinea pig heart do not present an objective evaluation of the activity of the drugs. Likewise, no data are reported on *in vivo* tests which would permit quantitative evaluation of drug efficacy. Dreyer alluded to the Lovejoy, Feinberg and Canterbury¹⁰ histamine flare test in man, and proceeds to cite his results of capillary permeability tests in rabbits. He neglects to state that Lovejoy, Feinberg and Canterbury in their tests on man report Trimeton to be distinctly more active than Neohetramine.

Analysis of Dreyer's blood pressure experiments with histamine reveals that this test does not adequately differentiate the efficacy of antihistamines. At one point, Dreyer suggests that thonzylamine is a hypotensive agent, whereas there is an implication that prophenpyridamine is pressor; yet elsewhere in the text the author distinctly states that prophenpyridamine, in common with other antihistamines, has both pressor and hypotensive properties dependent upon the dosage administered.

As shown in Table I, Chlor-Trimeton Maleate is clearly outstanding in that it has the greatest activity of the large series of antihistamines studied.* Since the acute toxicity of Chlor-Trimeton Maleate is comparable to that of the other agents, its therapeutic index and relative safety are the highest

*We have since tested every new antihistamine as it became available and still find Chlor-Trimeton Maleate to be by far the most active.

TABLE II. COMPARATIVE EXPERIMENTAL AND CLINICAL ACTIVITY
OF SEVERAL ANTIHISTAMINES

Antihistaminic Drugs	Relative Index of Activity in the Guinea Pig	Clinically* Effective Dose in Man	Relative Index of Clinical Activity
Chlor-Trimeton (chlorprophénopyridamine maleate)	100.0	mg/70 Kg 2 to 4	100.0
Trimeton (prophénopyridamine)	9.3	10 to 25	17.0
Neo-Antergan (pyramisamine maleate)	5.6	25 to 50	8.0
Histadyl (phenylpyramine—HCl)	3.5	50 to 100	4.0
Benadryl (diphenhydramine—HCl)	3.5	25 to 50	8.0
Thephorin (phenindamine)	4.4	25 to 50	8.0
Pyrbenzamine (tripelennamine—HCl)	4.4	25 to 50	8.0
Neohetramine (U.ozylan inc—HCl)	1.0	25 to 100	4.8
Antistine (phenazoline—HCl)	0.4	50 to 100	4.0

*Based on dosage recommendations in published clinical reports.

in the group. These values are 60 times the corresponding ones for Neohetramine, and 125 times those of Antistine.

Dreyer administered 50 mg/Kg of Chlor-Trimeton Maleate to guinea pigs, which represents 333 times the oral effective dose 50 without untoward effect, and this confirms the remarkable safety of the drug. In contrast, if one administers as little as 30 times the oral effective dose 50 of Neohetramine, 50 to 65 per cent of the guinea pigs die according to oral toxicity data on Neohetramine as published by Reinhard and Scudi,¹⁴ and this is confirmed by our own data (Table I).

The outstanding safety of Trimeton and Chlor-Trimeton Maleate has been further verified by extensive chronic toxicity studies in rats and dogs. Lifetime oral toxicity tests¹⁵ in rats conducted for three generations and similar studies in dogs continued for two generations have revealed the absence of any toxic or cumulative effects.

The validity of the animal experiments summarized in Table I is verified by the remarkable parallelism between the experimental and clinical activities of several antihistamines as shown in Table II. Based on quantitative experimental data, Trimeton has been shown to have superior efficacy and safety as compared with the older antihistamines. Extensive clinical research by and the experiences of numerous physicians confirm this superiority.^{2,6,11,12,13,15,16,20,21} Chlor-Trimeton Maleate is the most effective of all antihistamines and has the highest degree of safety of those evaluated to date. These laboratory findings regarding Chlor-Trimeton Maleate have been borne out by clinical reports.^{1,4,10,22}

SUMMARY

A review of the literature shows a remarkable parallelism between the therapeutic indices obtained in the laboratory and the excellent clinical

results obtained with Trimeton (prophenpyridamine) and Chlor-Trimeton Maleate (chlorprophenpyridamine maleate).

Using guinea pigs as test animals, oral toxicity and antihistaminic activity tests were performed on nine commonly used antihistamines. The therapeutic indices were: Chlor-Trimeton Maleate, 1,500; Trimeton, 180; Neo-Antergan, 116; Histadyl, 115; Benadryl, 70; Thephorin, 58; Pyribenzamine, 47; Neohetramine, 26; and Antistine, 12.

All these findings may be attributed to the unique chemical structures of Trimeton and Chlor-Trimeton Maleate.

Experimentally the relative safety of Chlor-Trimeton Maleate and of Trimeton is greater than any of the other drugs tested.

The relatively greater safety and efficacy of Chlor-Trimeton Maleate and Trimeton by comparison with other antihistamines as indicated in the laboratory have been borne out by numerous clinical reports.

2 Broad Street

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ALLERGY TO SO-CALLED "INERT INGREDIENTS" (EXCIPIENTS) OF PHARMACEUTICAL PREPARATIONS

HERON G. RANDOLPH, M.D., F.A.C.A.

Chicago, Illinois

AN excipient, according to Webster's Dictionary, is "an inert substance used in preparing remedies in order to give them a suitable form or consistency."

The major excipients used for binding the ingredients of pills, tablets, et cetera, include corn starch, milk sugar, gum acacia, gum tragacanth, licorice powder, flour, sugar and various chemicals.

Additional potentially allergenic materials employed in pharmacy in the manufacture of tablets, powders and capsules, as granulating agents, lubricating and disintegrating agents, flavorings and ingredients of coatings and capsules, include glucose, pectin, agar, gelatin, honey, gum karaya, casein derivatives, cocoa butter, chocolate, fresh eggs, corn oil, soy bean oil and olive oil.

During the past three years inquiries have been made of the principal manufacturers of encapsulated vitamins, and the following list of materials pertinent in this connection have been named as occurring in the capsule or filling of such medications: corn starch, corn sugar (glucose), granulated sugar, "wheat product," pork gelatin, acacia, beeswax, corn oil, cottonseed oil, soy bean oil, peanut oil and sesame oil.

Flavoring agents employed in prescription writing include such food items as syrup of cacao, raspberry, cherry, orange, rhubarb, cinnamon and sarsaparilla.

Non-aqueous vehicles for injectable medicinals include gelatin and oils of peanut, sesame and almond.

Manufacturing processes of official preparations not infrequently employ allergenic food stuffs or their derivatives. For instance, the current pharmacopoeia (XIII) permits the use of liquid glucose (derived from corn) and malt preparations (derived from barley and which, as a rule, are allergenic for the wheat-sensitive patient) as solid extracts. Corn starch, lactose, sucrose and powdered licorice (*glycyrrhiza*) are permitted as powdered extracts. Tinctures and alcoholic extracts of drugs may prove to be allergenic in certain instances, as the alcohol is usually derived from grain and it is recognized that cereal-sensitive patients are frequently intolerant to grain alcohol. To our knowledge the allergenicity of pure samples of alcohol has not been carefully studied in known cases of sensitivity to corn, wheat, malt, et cetera.

It immediately becomes apparent that these lists, although by no means complete, contain many common allergenic foods. Furthermore the man-

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facturing pharmacists are under no legal or other obligation to list such ingredients on the labels of their products. The Food and Drug Administration is interested only in the active ingredients of medicinal preparations, there being no stipulation regarding the labeling of excipients and diluents, many of which are of considerable interest to the allergist.

The most frequently encountered clinical problems in dealing with pharmaceutical preparations for allergic patients occur with those individuals highly sensitive to corn or milk.

CORN AS AN EXCIPIENT

Corn starch is the most widely used of all inert ingredients in pharmacy. A physician is safe in assuming, at least until disproved by the statement of the manufacturer, that corn starch is present in all tablets designed for ingestion.* The first instance of the allergenicity of corn employed as an excipient and diluent was reported by Rinkel¹⁹ in 1944, although he²⁰ had made the observation in 1936 that the ingestion of corn contained in a proprietary medication employed for the relief of coughing actually increased this symptom. The patient, known to be corn sensitive, failed to respond to corn avoidance until he ceased taking this medication. Readministration of the preparation resulted in the recurrence of allergic symptoms, shown unequivocally to have been due to the corn content of the medication.

Case E. R., a woman, aged fifty-four, previously reported in brief,¹³ had been subject to severe intermittent headaches for fifteen years and status migrainous for the past decade. This had been associated with constant dizziness to the point that she was unable to leave her home for months at a time and on many days had been unable to walk. When first seen she also complained of a debilitating degree of weakness, alternating constipation and diarrhea and a chronic dermatitis of her hands.

Cutaneous and intracutaneous tests with inhalants revealed that she was sensitive to house dust. She was shown to have a widespread allergic response to foods as indicated by the precipitation of several acute clinical reactions following individual food tests (Rinkel's²¹ technique as confirmed by Randolph and Rawling¹¹). Corn proved to be one of her most troublesome food allergens. With the maintenance of dust therapy, the complete avoidance of corn in addition to other incriminated foods and the rotation of tolerated foods in her diet, her allergic symptoms were effectively relieved for a period of several months, except as she inadvertently encountered a source of one of her food allergens. This was accomplished in the absence of all medication.

Then, for reasons unexplained at the time, she noticed a gradual recurrence of her chronic fatigue, followed in turn by dull constant headaches. It was first thought that her known food allergens had not been completely eliminated but sources of exposure could not be detected. It was then assumed that she had developed a sen-

*A simple test to determine the presence of starch in tablets or powders consists of applying a weak solution of potassium iodide or tincture of iodine. The presence of starch is indicated by the development of a bluish, purple color. It should be emphasized that this test is not specific for corn starch but a positive reaction is presumptive evidence that it is present in a preparation unlabeled in respect to excipients in view of the fact that it is by all means the most common vegetable starch employed for this purpose. Flour, tapioca or arrowroot starch, to name others occasionally employed as excipients, will also give a positive iodine reaction.

One is sometimes aided in identifying a given type of starch by the microscopic appearance of the individual granules. Excellent illustrative plates exist in many older texts.^{8,10}

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sitivity to a new food, but all questionable items in the diet, as revealed by her food diary, were checked by performing individual food tests and found to be compatible. By a fortuitous circumstance, she omitted her tablet of desiccated thyroid for a period of four days; this medication had been re-prescribed two months earlier because of the suggestive symptoms of hypothyroidism and the finding of a basal metabolism of minus 16 per cent. However, when it had been taken prior to the establishment of her allergic diagnosis, it had failed to alter the course of her chronic fatigue or other symptoms. With omission of this tablet, she felt immeasurably improved by the end of the third day.

The same tablet was then reintroduced at noon on the fifth day of avoidance and was followed by marked yawning and somnolence. She lapsed into a stuporous sleep forty-five minutes after taking the tablet and continued to sleep all the afternoon and evening. Residual fatigue persisted the following day. The tablet in question gave a positive iodine test for starch and was found to contain corn starch as an excipient, on the statement of the manufacturer.

The patient was then placed on desiccated thyroid free of corn starch and other excipients commonly associated with allergic reactions** and has tolerated this preparation for the past year.

On another occasion she had a gradual return of her fatigue and headache shortly after starting to take tablets from an old supply of ferrum reductum.

One other time when hospitalized for the surgical removal of a papilloma, she was given aspirin for the relief of local pain and within an hour complained of an excruciating headache.

She has tolerated ferric ammonium citrate and corn-free aspirin for many months. Several different times she has been given tablets of thyroid or aspirin "blindly" without knowledge as to whether or not they contained corn starch, and on each occasion she was able to detect the presence of the corn starch excipient as a result of her symptom reaction. In the numerous times this was tried, not once did she incriminate the presence of corn products when they did not exist in the test tablet.

Case M. A., a woman, aged twenty-nine, had complained of the symptoms of chronic nasal allergy, intermittent headaches associated with myalgia of the posterior cervical muscles,¹⁵ childhood and fall hay fever for the past three years, complicated by seasonal asthma.

She was found clinically sensitive to house dust and several fall pollens for which she was specifically treated.

Because of the history of noticing itching of her nose when ironing, she was immediately suspected of being corn sensitive and prepared for an individual food test. Although she had her usual continuous mild headache prior to the experimental feeding of corn meal and corn sugar, she noticed a sharp accentuation of the head pain in association with somnolence and rhinorrhea beginning five minutes after the trial ingestion. Within an hour she developed a severe chill, remaining chilly and complaining of generalized aching throughout the remainder of the afternoon. This clinical reaction, simulating the grippe, required four days to subside.

With continuation of specific inhalant therapy and the avoidance of corn and other proven food allergens, she had no troublesome symptoms until the onset of the 1947 ragweed pollen season, at which time she developed moderately severe hay fever. A well known antihistaminic drug was prescribed in the hope of diminishing her symptoms, but she became worse immediately after taking each tablet. After a few days of this therapy she started to have severe and constant asthma in addition to hay

**A line of common pharmaceuticals available in tablet form excluding corn and other major allergenic excipients is available from the Upjohn Company, Kalamazoo 99, Michigan, under the trade name, "Abergic."

Of the antihistaminic drugs, Benadryl in the form of the elixir and 50 mg. kapseal (Parke, Davis), Pyrrolazole (Upjohn), Hydryllin (Searles) and Histadyl (Lilly) are known to be currently free of the major allergenic excipients.

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fever and a recurrence of her troublesome headaches. Her symptoms promptly improved with the cessation of the drug in spite of continuing high ragweed pollen counts. The same medication was started again after four days of avoidance; this was again followed by severe headaches and coughing. At this point it was ascertained from the manufacturer that the tablet contained corn starch as an excipient.

The pharmaceutical firm kindly made available the antihistaminic drug in crystalline form; this as well as the crushed tablets were placed in colored capsules and administered to the patient experimentally without her knowledge of which contained the excipient. She developed a recurrence of her coughing and headache only following ingestion of the preparation containing corn.

One other corn-sensitive patient, allegedly sensitive to sulfadiazine, in that its administration was invariably followed by rhinitis and coughing, has been able to tolerate the Abergic brand without untoward effects.

Several other corn-sensitive individuals on a regimen of avoiding corn and products derived from it have commented spontaneously on the greater effectiveness of corn-free aspirin in relieving their aches and pains in comparison with the standard commercial product.

Observations bearing on the allergenicity of corn sugar (glucose and dextrose) have recently been presented.¹⁶ The writer has seen two highly corn-sensitive patients in which the use of lozenges was suspected of causing a recurrence of their symptoms of the type due to corn sensitivity. In each instance, the lozenges were found to contain corn sugar.

Corn oil, in the amount ordinarily employed in pharmaceutical preparations, has not been proved to cause symptoms in corn-sensitive patients. However, certain corn-sensitive individuals have been observed to develop symptoms following the experimental or accidental ingestion of corn oil. The oil appears to be the least allergenic of all the corn products.

MILK AS AN EXCIPIENT

Speaking generally, one may assume that tablets designed to be dissolved for hypodermic injection contain lactose or milk sugar. Because of its relatively low deliquescence, milk sugar is the favorite diluent to give bulk to powders and to mix with powdered medicinals for filling capsules. That lactose is capable of eliciting allergic symptoms in highly milk-sensitive individuals is attested by the following cases:

Case M. H., a woman, aged thirty-one, had been subject to episodes of nausea, vomiting and diarrhea for eight years; severe fatigue and generalized muscle soreness and headache for three years; and unexplained urgency and frequency of urination for three months. She had been receiving frequent hypodermic injections of codeine for relief of her headaches and cervical myalgia. For a period of several months she had noticed a progressively severe degree of local pruritus at the sites of her codeine injections.

In the avoidance of milk in preparation for an individual food test, she was changed from the standard codeine prepared from tablets containing milk sugar to a solution of codeine crystals dissolved in saline. She promptly commented on the absence of itching at the sites of her injections and on the greater effectiveness of the drug in relieving her pain and aching, although she was receiving a constant dose.

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An individual food test with milk was followed in eight minutes by the onset of sharp epigastric colicky pain which radiated through to mid-back. A second feeding of milk an hour later was associated with a sharp accentuation of her previous pain. Her gastrointestinal reaction persisted through the night and for a period of three hours was associated with generalized pruritus. All symptoms had subsided by the following morning except for residual abdominal soreness.

With the complete avoidance of milk and numerous other incriminated foods, she has had complete relief of her pruritus and has shown marked improvement of other symptoms. For a period of several weeks during her diagnostic studies she remained subject to intermittent headaches for which codeine was administered. During this interval she was treated both with lactose-containing codeine and milk-free codeine without a knowledge of which type she was receiving. Invariably, she was able to state whether or not the injection contained lactose as a result of the associated local pruritus and the effectiveness of the analgesic action.

Parallel subcutaneous and parallel intradermal injections of the varieties of the drug failed to reveal any significant differences in the relative sizes of the local reactions, but in each instance she was able to identify the injection containing lactose by the presence of intense local pruritus.

The case of I. K., a nurse, aged twenty-three, subject to chronic incapacitating headaches, has been previously reported¹⁷. She was found to have an exceedingly high degree of milk sensitivity. On several occasions the inhalation of the fumes of cooking milk (osmyls) was sufficient exposure to produce an acute allergic response.

Shortly after her original diagnosis was made, the inadvertent ingestion of small amounts of milk or butter would be followed by the sudden onset of a violent headache. She learned that such attacks could be materially reduced in severity if a hypodermic injection of codeine was administered with the first warning of the episode, but codeine was not nearly as effective if she waited until a needle and syringe could be sterilized. Consequently, she was supplied with a rubber stoppered vial of codeine solution containing crystals of codeine phosphate dissolved in normal saline. She not only experienced no abnormal local reaction from these injections but obtained the customary analgesic and sedative actions from the drug.

At this point (that is, at the time her case was reported), she moved to another section of the country and very soon began having a recurrence of her chronic headaches for which she continued to take codeine. She began noticing a gradual change in its action in that the injections became relatively ineffective in relieving her head pain, and instead of obtaining the expected sedative action from the drug, she noticed that it seemed to make her more tense, irritable and excited. She obtained transitory and partial relief of her headache immediately following an injection but then her head pain would become more severe and the more codeine she took the more excited she became. She had also developed very large local reactions from the injections.

It then developed that she had been using a codeine solution prepared from tablets rather than crystals. Without informing the patient that codeine tablets usually contain lactose as an excipient, an identical dose of the drug prepared from crystals dissolved in saline solution was administered. She subsequently commented, spontaneously, that she had obtained more relief of her pain from that injection than from any other she had received for two years and immediately inquired as to how it had differed. She further observed that for the first time in months she did not have a local reaction from the injection.

In view of the extreme severity of her reaction to milk, she was not subjected to additional experimentation with codeine preparations containing lactose.

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GUM TRAGACANTH AS AN EXCIPIENT

Brown and Crepea¹ recently presented a case of asthma and urticaria due to gum tragacanth employed as an excipient in a well known antihistaminic tablet. They suggested that the minor ingredients of a given pharmaceutical preparation should be carefully investigated before attributing sensitivity reactions to the principal ingredient. Allergic reactions from the inhalation of gum tragacanth particles have been emphasized by Gelfand.²

GUM ACACIA

To our knowledge, gum acacia or gum arabic has not been incriminated as a cause of allergic reactions as an excipient in acacia-sensitive individuals, but Spielman and Baldwin²⁴ have pointed out that acacia is commonly used as an emulsifying agent in the preparation of pharmaceutical preparations. The allergenicity of acacia has also been emphasized by Maytum and Magath,¹² Studdford,²⁶ Levin,¹¹ and Feinberg and Schoenkerman.⁵

GUM KARAYA

Neither has gum karaya been specifically incriminated as a cause of allergic reactions from its use as an excipient in medicinal tablets. Karaya sensitivity, first reported by Bullen⁸ and confirmed by Feinberg,⁶ Bowen² and Figley,⁷ is contained in many laxatives and dentifrices.

LICORICE (GLYCRRHIZA)

Although instances cannot be found where glycyrrhiza has been reported to cause allergic symptoms from its occasional use as an excipient, it is known to sensitize and this possibility should be kept in mind. The author has a case of sensitivity to licorice in a patient highly sensitive to other legumes.

OTHER SUGARS

The allergenicity of corn sugar (dextrose and glucose) and milk sugar (lactose) has previously been discussed.

In the writer's experience, beet sensitivity is common in areas where beet sugar is used as the principal source of sugar and is not an infrequent allergen in other regions. The ingestion of granulated beet sugar will cause symptoms in many beet-sensitive patients, confirming the experience of Rinkel²² and Zindler.²⁸ The use of beet sugar in the simple syrup of prescriptions has resulted in the production of allergic symptoms in patients known to be beet sensitive, whereas the same prescriptions were tolerated in the absence of beet sugar.

Sensitivity to cane was first emphasized by Coca.⁴ Although less common than beet sensitivity, it is being recognized with increasing frequency since it has been suspected as a cause of symptoms in all undiagnosed patients and tested by means of the individual food test technique^{14,21}.

Several instances have been proved as a result of this diagnostic approach. Prescriptions containing cane sugar in the form of simple syrup have been shown to cause allergic symptoms in these individuals when all other ingredients of the prescriptions were test negative.

The practice of using sucrose in simple syrups, regardless of its origin, makes it necessary for physicians dealing with patients allergic to one or more sugars to stipulate in writing the prescription the type of sucrose that he desires to be employed.

GELATIN AS AN EXCIPIENT

Contrary to the alleged non-antigenicity of gelatin,^{25,27} Rinkel²³ has observed several instances of allergic reactions to the ingestion of gelatin in beef- and pork-sensitive patients. The writer¹⁸ recently reported clinical reactions to the ingestion of commercial gelatin in three of four highly beef-sensitive individuals.

The patients were diagnosed specifically by means of individual food tests with beef, and in each instance severe allergic symptoms followed the experimental feeding of this food. They were then tested by means of the individual food test technique with one quarter ounce of gelatine (Knox) dissolved in warm water. Three of the four developed unmistakable symptoms immediately following the test feeding; in each instance the symptom response was similar to that associated with the original individual food test with beef. A week later three of the same patients ingested 150 ml. of gelatine prepared for intravenous use (Knox), and two of the four (the same two who had reacted to the ingestion of commercial gelatin) also developed unmistakable symptoms.

In additional unpublished observations, the above patient with the most marked reaction to the ingestion of gelatin prepared for intravenous use was retested with the ingestion of a similar amount of another brand of beef gelatin at a time when she was still exquisitely sensitive, as judged by the fact that she reacted with clinical symptoms from eating pork cut on a beef butcher block. Ossine gelatin (Wilson) prepared for pharmaceutical purposes failed to produce a clinical reaction. Another exceedingly pork-sensitive individual, as judged by the development of rhinitis and migraine on several occasions following the inhalation of cooking pork, also failed to develop a demonstrable symptom response after the ingestion of pork gelatin (Wilson) prepared for the pharmaceutical trade.

In summary, it may be said that at least certain brands of gelatin may cause symptoms in the highly beef- or pork-sensitive patient. This would appear not to be invariably true, and individual cases should be studied in their possible reaction to individual preparations.

Instances have not been observed by the writer where gelatin employed as an excipient has caused reactions in known beef- or pork-sensitive patients.

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DISCUSSION

It is generally recognized that the absolute avoidance of specific foods is an essential requirement both in the diagnosis and treatment of allergic individuals highly sensitive to those foods, otherwise the specific diagnosis may be in error and the treatment ineffective. For example, if one diagnoses food allergy by means of individual food tests, a prime requirement for interpretation of such tests is that the food in question be avoided for a short period prior to the experimental feeding. If one employs restricted diets in diagnosis, relief of symptoms may not ensue if a given allergenic food is continued to be ingested in the form of an excipient.

Numerous instances have been cited in which, although the diagnosis had been correct, the incomplete avoidance of the allergen in question due to its continued ingestion as an excipient, failed to result in the expected amelioration of clinical symptoms. This course of events is apt to lead one to the false conclusion that the specific diagnosis is incomplete and not infrequently results in an unnecessary prolongation of diagnostic studies. Furthermore, and from the long range standpoint, one cannot expect the degree of sensitivity to a particular food to subside significantly, even with the avoidance of dietary sources, if it is received several times daily in medicinal sources.

Inasmuch as it is frequently desirable and sometimes necessary to continue the use of medications during periods of specific diagnosis and therapy, it behooves the clinician in this field to become familiar with the excipients employed in the medications that he is accustomed to using. The only way in which this may be accomplished at present is by the cumbersome procedure of addressing inquiries directly to the manufacturing pharmacists.

Even though a physician is familiar with the food stuffs that he is prescribing in medications, it frequently becomes a difficult task to protect his patient from specific exposures. The problem can be handled reasonably satisfactorily where all medications are prescribed by a single individual solely responsible for the patient's health. Difficulties are apt to arise in instances where this responsibility is shared with other medical colleagues, and, particularly, if the patient is inclined to indulge in self-medication.

The greatest hazard experienced to date has been in handling the allergic patient who requires hospitalization. Simply ordering a corn-free regimen, for instance, is not sufficient, due to the fact that interns and hospital pharmacists are ordinarily not familiar with the distribution of excipients in pharmaceutical preparations, and, more importantly, neither have ready access to this data. Although a given intern may be made familiar with this problem, such precautions are apt to break down when he is off duty or when he is succeeded by a fellow house officer.

This emphasis on medications as food and, for that matter, even the restriction of specific food allergens, has no parallel in the diagnosis and

treatment of other medical conditions encountered in the general hospital. The infinite care to accomplish such a program does not fit harmoniously with other hospital tasks. As a consequence, blunders from the standpoint of the specific elimination of foods are very apt to occur, even though the physician in charge attempts to anticipate all such possibilities. A striking example of this type of error may be cited. A patient with sufficiently severe gastrointestinal symptoms to require hospitalization was shown to be sensitive to milk, as evidenced by the relief of his digestive disturbances following the avoidance of this food and the reproduction of distressing symptoms in association with its experimental ingestion. Explicit orders were written proscribing all dairy products and limiting medications to those known to be free of lactose. Furthermore, the patient was fully aware of the deleterious effects of milk and had been thoroughly briefed in the sources and possible ways in which he might encounter this food.

On making his evening rounds, the writer was confronted with an angry, violently ill patient who had previously been recovering satisfactorily. A milk and molasses enema had been ordered by the intern, the order had been checked by the floor nurse, then assigned to and executed by the orderly. Within the first few minutes of this "treatment," the patient complained bitterly of pain, withdrew the tube and demanded to know what he had been given. This unfortunate experience precipitated several days of acute illness and unnecessarily prolonged his hospitalization. He was finally persuaded not to bring suit against the institution.

The present chaotic condition in respect to the recognition of the clinical importance of excipients is exemplified by the fact that one popular anti-histaminic drug, even though designed for the use of allergy patients, contains milk sugar in one size dosage but does not contain this excipient in the other. It is also revealing that neither the Food and Drug Administration nor the editors of the Pharmacopoeia have made any effort to regulate this aspect of drug manufacture, referring to the food products under discussion merely as "inert ingredients." Descriptions of accepted products by the Council of Pharmacy and Chemistry of the American Medical Association for inclusion in New and Non-official Remedies do not contain this information even though it has been supplied by the manufacturer.

The purpose of this presentation is not to injure any particular preparation or pharmaceutical firm but to call to the attention of the medical profession, the Council of Pharmacy and Chemistry of the American Medical Association, the manufacturing and dispensing pharmacists, the Food and Drug Administrator and the editors of the United States Pharmacopoeia, that the physicians dealing with food-sensitive allergic patients not only need to be informed but have the right to know the food ingredients of the medications that they are prescribing. It is suggested that pharmaceutical firms change their excipients and binders to less allergenic substances and that they state the composition of the "inert" as well as the active ingredients of their preparations.

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SUMMARY

Various food products, designated as "inert ingredients," are employed as excipients or binders in the manufacturing processes of practically all tablet medications and in many other forms of pharmaceutical preparations. Neither by common practice nor current regulation are these food ingredients labeled on the package.

Certain patients, highly sensitive to such common foods as corn and milk for instance, may have allergic symptoms precipitated by the ingestion or injection of medicinals containing these specific excipients.

Illustrative cases are cited.

Addendum: Four patients highly sensitive to corn have been observed to have symptoms identical to those produced by the test ingestion of corn or corn products after the administration of penicillin G.

A reaction consisting of severe headache with nuchal myalgia, nausea, vomiting and diarrhea occurred each of four times in one adult; a child age seven developed abdominal cramps and an elevation in temperature to 101.0 degrees F. on each of two occasions and a child three years of age developed severe diarrhea after each attempt to administer penicillin G by injection. Penicillin in oil or aqueous form produced these responses. Another adult developed an acute rhinitis following the use of penicillin G in the form of troches which also contained dextrose of corn origin.

The fungus, penicillium, from which penicillin is harvested, is usually grown on corn steep liquor. In as much as the first three patients have tolerated penicillin O (prepared by the Upjohn Company, Kalamazoo, Michigan, from non-corn nutrient sources and not containing additional corn in the form of excipients or diluents) when administered by injection and the fourth has tolerated corn-free penicillin O troches, it is strongly suggested that penicillin as ordinarily available commercially carries the allergenicity of the corn steep liquor, upon which it is grown, into the manufactured product.

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PRECIPITIN REACTION

(Continued from Page 507)

statistics and examples of the different groups are shown, stressing the practical value of microprecipitin determination in diagnosis of allergic disease.

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COMPARING THE IRRITANT ACTION OF SOAPS

LOUIS SCHWARTZ, M.D.

Washington, D. C.

SOAPS are the oldest, most universally used, and, all things considered, the most satisfactory means of removing soil from the normal human skin. They are the first of the synthetic detergents.

There are various theories as to how soaps remove soil from the skin, the most commonly accepted of which is the one that soap cleans because of its power to emulsify and suspend dirt particles in such form that they may be floated off the skin. The soap molecule consists of a water-soluble end (the alkali) and an oil-soluble end (the fatty acid radical). When a soap solution contacts dirt particles the soap molecules surround the particles, each with its oil-soluble end turned so that it is in contact with the dirt particle. The water-soluble ends project out into the solution. The dirt particle is in effect floated by a multitude of adhering soap molecules and is thus prevented from settling out of the soap solution or redepositing on the surface.

Soaps, by their action of removing soil from the skin, also have a secondary deodorant action because they remove from the skin substances which give off offensive odors. Substances which give off offensive odors may consist of (1) foreign matter deposited on the skin, (2) secretions of the skin glands which have decomposed on the skin, (3) abnormal secretions of the skin glands having an offensive odor.

Soaps, as well as other skin cleansers, not only act on the secretions of the skin and soil deposited on the skin, but also have a definite action on the skin itself. The alkaline solution tends to soften, loosen and dissolve the keratin layers of the skin. Not only do soaps emulsify, dissolve and remove foreign oils, but they tend to remove the natural oils, fats and waxes from the skin, thus tending to drying, thinning and shrivelling of the skin. Hence the prolonged action of soaps may result in dermatitis, especially in the case of persons having naturally dry skins. Therefore, the prolonged immersion of the skin in low concentrations of soaps or exposures of the skin for shorter periods to strong concentrations of soaps and other skin cleansers may result in a dermatitis due to primary irritation. In addition to this, some skins may become allergic to alkalis or to certain fatty acids and their salts. Certain soaps are more likely to irritate the skin than others, as for instance it is generally recognized that potassium soaps are more likely to irritate the skin than sodium soaps, and that soaps made of coconut oil are more likely to irritate the skin than soaps made from tallow or olive oil.

A large internationally known manufacturer of soap was about to

This paper is the result of patch tests on 200 humans comparing the irritant action of a new deodorant soap with a toilet soap base and with a deodorant soap on sale for many years. This investigation was sponsored by Armour Toiletries, Chicago, Illinois.

Dr. Schwartz is an Honorary Fellow of The American College of Allergists.

place on the market a new deodorant soap. It contains Hexachlorophene (bis-3,5,6-trichloro-2hydroxy phenyl methane), an antiseptic and germicide which, when added to soap, has been proven by experiments to rid the skin of far more germs than can the soap itself.^{3,10,11,12} It has also been shown that repeated washing with a soap containing Hexachlorophene will cause an accumulation of this chemical on the skin and thus prevent the multiplication of the bacteria which may not have been destroyed or removed.^{2,9} Since the offensive odor of the perspiration has been shown to be mainly due to bacterial decomposition of the naturally odorless skin excretions (perspiration, sebum) which are deposited and accumulate on the skin,^{4,5} especially in the axillae, the groins, under the breasts, and other skin folds, it was thought the continued use of a soap containing Hexachlorophene, which so markedly reduces the bacterial flora of the skin, would prevent the decomposition of the skin excretions and hence act as a deodorant soap. Unpublished experiments performed by a well-known consulting laboratory have actually proved this to be the case.¹

Before placing the new deodorant soap on public sale, the manufacturers, wishing to safeguard against dermatitis, compared its action on the skin with soaps which have long been on the market without causing any undue amount of dermatitis, and this paper records the experiments devised to make this comparison.

In 1940, the author published a method for testing the possible skin-irritant properties of new substances before placing them on sale.⁸

This method consists of first performing two series of patch tests, about ten days apart, on at least 200 humans with the new substance, and using as a control patch a similar substance that has long been in public use without causing any undue amount of dermatitis. (This recognizes the fact that there is scarcely any substance to which someone may not be sensitive or become sensitized).

A comparison of the positive reactions obtained from the test product with the positive reactions obtained from the product long on the market without causing any undue trouble is made. If there are no more reactions from the test product than there are from the product long on the market, then the test product can be placed on trial sale in a small community, 5,000 to 10,000 people, for a month or more for the purpose of finding the skin-irritant potential. The results of this test will determine whether the product can be placed on the general market without endangering the public.

The above-described method was devised, having in mind fabrics for wearing apparel in which the concentration of the chemicals is constant and evenly divided throughout the fabric.

It is apparent that when liquids, oils, fats or powders are to be tested, comparative patch tests, in order to be of value, must be performed with equal amounts of the substances to be compared, placed on equal areas of skin, and on similar places on the body. (The reactivity of the skin on

different parts of the body may vary because of normal anatomical and physiological variations).

Such a method of comparative patch testing can easily be performed by the standardized patch test devised by the author.⁶

With this method of patch testing, definite amounts of substances can be applied to constant or definite and similar areas of skin, for definite periods, thus enabling a comparison of the skin-irritant properties of several substances. The effect on the skin of various concentrations of the same substance can also be determined.

The standard Schwartz patch consists of a square piece of flannel 3 sq. cm. in area, to which 0.2 c.c. of a liquid is applied with a graduate pipette, or hypodermic syringe or an eye dropper. The moistened flannel is placed on the skin, covered with a piece of elastic fabric of a special pattern, in the center of which there is an insulating square piece of uncoated cellophane (regenerated cellulose) measuring 1½ inches on each side. The cellophane is placed directly over the moist flannel. When patching with greases, definite amounts of the greases are spread over the flannels. The same applies to powders.

Thresholds of sensitivity can be determined by the application of ascending amounts of the liquid, grease or powder. The time factor can also be controlled.

The above-described method of patch testing was used to compare the effect on the skin of a new deodorant soap, with the effect on the skin of a base toilet soap and with a deodorant soap which has been on the market for many years.

In 1934 Schwartz⁷ prepared a special soap made from sodium hydroxide and first pressing of olive oil, and found that a 3 per cent solution placed on the skin for twenty-four hours, as a patch test, would in most cases cause only a slight branny desquamation. Therefore, it was decided to apply as the first or sensitizing patch a 3 per cent solution of each of the three soaps.

The compositions and pH of the applied soap solutions were as follows:

Base soap consisted of 80 per cent of a sodium hydroxide, tallow soap plus 20 per cent of a sodium hydroxide, coconut oil soap; pH 10.3.

New deodorant soap consisted of the above base soap to which was added 2 per cent Hexachlorophene and 1 per cent perfume; pH 10.2.

Control deodorant soap was a soda tallow-coconut soap, plus a chemical deodorant; pH 10.2.

The results of the patch tests would show the effect on the skin of the action of the additives to the base soap and also give a comparison of patch tests with the test soap, with patch tests with the same concentrations of the well-known control deodorant soap (which has been sold for many years without undue harmful effects).

Two hundred white subjects were used. These were about two-thirds male and one-third female.

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The following technique was used: 0.2 c.c. of a 3 per cent solution of soap was applied to a piece of absorbent flannel 3 sq. cm. in area. This was sufficient to wet the flannel without having the solution drip out of it. The wet flannel was applied to the skin of the upper arms, forearms, back, or thighs as desired by the subjects. However, all three patches were applied to similar locations on the same subject. The flannel was sealed on the skin with a piece of elastic fabric to which adhered a piece of uncoated cellophane 1½ in. sq. which covered the wet flannel. The patches were removed at the end of twenty-four hours and the reactions noted.

193 subjects returned for reading of reactions.

Degree of Reaction	++	+	?	-
Base Soap.....	0	180	0	13
New Deodorant Soap	0	182	0	11
Control Deodorant Soap	2	184	0	7

This first test showed that a 3 per cent solution of these soaps permitted to remain on the skin for twenty-four hours under a sealed patch will cause reactions on nearly all subjects, i.e., is a primary skin irritant.

In order to determine what concentration of the soaps was to be placed on the skin in the second series of tests (to determine sensitization), six of the subjects who had undergone the first series of tests, and reacted to all three patches of 3 per cent strength, were patched with 1 per cent and 2 per cent solutions of the base soap and of the control deodorant soap using the technique described above. The patches were removed at the end of twenty-four hours. All the subjects showed reaction to the 2 per cent solutions. Only three subjects showed reactions to the 1 per cent solution. Therefore it was decided that 1 per cent solutions of the three soaps were to be used in the second series of patch tests to determine the number sensitized by the first series.

The second series of patch tests were applied fifteen days after the first series. The same technique was used as in the first series.

193 subjects were patched with 1 per cent solutions of the three soaps according to the technique described above. The pHs of these solutions were: Base Soap—9.9; New Deodorant Soap—9.9; Control Deodorant Soap—9.9.

The patches were removed at the end of twenty-four hours and the reactions were read as follows:

Degree of Reaction	++	+	?	-
Base Soap	5	102	36	50
New Deodorant Soap.....	0	51	38	104
Control Deodorant Soap	6	114	32	41

Twenty-four hours after the removal of the patches, the subjects were again examined for delayed reactions. At this examination the following gradations of the reactions were made.

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Results of reaction readings twenty-four hours after removal of second series of patches:

Degree of Reaction	++	+	?	-
Base Soap	1	89	26	65
New Deodorant Soap.....	0	33	25	123
Control Deodorant Soap.....	4	95	24	58

It will be noted that there were fewer reactions twenty-four hours after the removal of the patches, than there were immediately upon their removal. This shows that the reactions which had disappeared twenty-four hours after the removal of the patches were definitely reactions of primary irritation.

The results of these tests showed that:

1. A 3 per cent solution of all three soaps remaining on the skin for twenty-four hours in the form of a standard covered patch test will cause reactions on more than 90 per cent of subjects.
2. A 1 per cent solution of the base soap under the same condition caused definite reactions on about 46 per cent (taking the final reading twenty-four hours after removal of one per cent solution patch).
3. A 1 per cent solution of the same base soap to which 2 per cent Hexachlorophene and 1 per cent perfume was added, caused definite reactions in only about 17 per cent under the same conditions.
4. A 1 per cent solution of the control deodorant soap caused definite reactions in about 51 per cent.
5. None of the subjects who showed no reactions to the first series of patches of the 3 per cent solutions showed reactions to the second series of patches of 1 per cent solutions.
6. There was no significant difference between the percentage of reactions to the base soap and to the control deodorant soap.

DISCUSSION

There were fewer reactions to the second series of patches than to the first series. This is unusual, but may be because all the subjects were soap users, and whatever sensitizations they could acquire to soap they had already acquired before the tests began. Or it may be that the sensitization which may have been acquired by reason of the application of the 3 per cent solution patches was more than counterbalanced by the fact that the second series of patches were only one-third the strength of the first series.

In the second series of patches there were less reactions to the new deodorant soap than to the base soap from which it was compounded despite the fact that in addition to the base soap the new deodorant soap contained 2 per cent of Hexachlorophene and a perfume. It may be possible that the sensitizing properties of 1:5,000 of Hexachlorophene (the amount contained in the second series of patches) would not show, where-

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as the superfatting of the soap by the presence of the essential oils of the perfume and by the Hexachlorophene may have reduced the irritant properties of the base soap.

CONCLUSIONS

1. The above described standardized method of patch testing can be used satisfactorily to compare the relative skin-irritant properties of various soaps.*
2. Although the closed patch tests, as described, show a considerable number of reactions among the test subjects, all of them use soap for the cleansing of the skin without any skin irritation. This shows that the closed patch test with soap is more irritant than actual usage of soap.
3. The base soap and the control deodorant soap, although showing more reactions under the above-described patch test conditions than the new deodorant soap, have been actually used by the public in large quantities for many years without any undue number of cases of sensitization.
4. The new deodorant soap showing considerably less reaction under the above described patch test conditions, should cause even fewer sensitizations when used by the public than do the base soap and the control deodorant soap (which has been on the market for many years).
5. Since this experiment was conducted, several million cakes of the new deodorant soap have been sold with no proven cases of sensitization having been reported from its use.

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*The relative primary irritant and sensitizing properties of other chemicals can also be ascertained by this method.

THE VARIABILITY OF ORAL ANTIHISTAMINIC THERAPY

HYMAN J. RUBITSKY, M.D., LEON LEVINSON, M.D., ELLIOTT BRESNICK, M.D.,
GEORGE RISMAN, Ph.D., and MAURICE S. SEGAL, M.D., F.A.C.A.

Boston, Massachusetts

IN the course of investigating the ability of various antihistaminic agents to prevent the decrease in vital capacity induced in some asthmatic patients by histamine, we have encountered three individuals who showed no such protective action following the oral administration of diphenhydramine or tripelennamine. In each case, the protecting capacity of the drug after parenteral administration was similar to that manifested by other patients, in whom no demonstrable impairment of antihistaminic activity was observed following their oral ingestion.

The technique of these studies has already been reported in detail.^{2,3,6} Essentially, it consists of observing the effect of a therapeutic or protecting agent in modifying or preventing the decrease in vital capacity induced by the administration of any bronchospastic agent, in this case histamine di-phosphate, given intravenously or as an aerosol. Injections or aerosolizations of the bronchospastic agent are repeated until the effect of the protecting agent has disappeared, when the decrease in vital capacity returns to the pre-protection levels. The degree of protection present at any time has been described in terms of the following equation:

$$P = \frac{C - E}{C \times 100},$$

where P = degree of protection in per cent, C = control decreases in vital capacity, measured prior to administration of the protecting agent, and E = the decrease observed when histamine is administered at any interval after the protecting agent has been given. We have considered protection values below 40 per cent of doubtful significance, in view of the many sources of error inherent in any technique of clinical assay. Both diphenhydramine and tripelennamine were administered orally and rectally in 50 mg. doses; the intravenous dose of tripelennamine hydrochloride was .25 mg. of diphenhydramine hydrochloride, 28 mg. All aerosols were produced in the Vaponefrin nebulizer. Six inhalations were

From the Department of Inhalational Therapy, Boston City Hospital, and the Department of Medicine, Tufts College Medical School. This study was supported by a grant from the United States Public Health Service.

Dr. Rubitsky is Resident in Medicine, Department of Inhalational Therapy, Boston City Hospital.

Dr. Levinson is Assistant in Medicine, Tufts College Medical School, Associate Fellow of the American College of Allergists.

Dr. Bresnick is a former Charlton Research Fellow and now Assistant in Medicine, Tufts College Medical School.

Dr. Risman is a Volunteer Assistant in the Department of Inhalational Therapy, Boston City Hospital, Fourth Year Medical Student, University of Pennsylvania.

Dr. Segal is Director, Department of Inhalational Therapy, Boston City Hospital; Assistant Professor of Medicine, Tufts College Medical School.

given as a dose. A 2 per cent tripeleannamine solution and a 1.4 per cent diphenhydramine solution were used for the aerosols.

Histories of the three individuals who did not exhibit protection following the oral administration of diphenhydramine or tripeleannamine are presented below.

Case 1 (G. Bro.).—This man, aged thirty-three, married, white, a street-car operator, was seen at the height of the ragweed season (1948) with moderate severe asthma and hay fever. His asthma was perennial, but was always worse in August and September. No previous or family history of allergy could be elicited. Positive intradermal skin tests were elicited to dust, to mixed feathers, and to dog and cat hair. In spite of large amounts of seven different oral antihistamines, no relief from his distressing hay fever and bronchospasm was obtained, even though drowsiness was frequently produced. The bronchospasm was relieved on a regimen of bronchodilator aerosols as needed and rectal aminophyllin two to three times daily, but the hay fever was so distressing as almost to incapacitate him.

On two occasions the oral administration of 50 mg of tripeleannamine resulted in no modification of the vital capacity response to subsequently administered histamine aerosols. When the same dose of tripeleannamine was administered rectally, 40 per cent protection against histamine aerosol was apparent within fifteen minutes, and protection became complete (100 per cent) sixty minutes after tripeleannamine had been administered rectally. Complete protection lasted for about sixty minutes and the degree of protection then decreased gradually, falling to 40 per cent again 165 minutes after tripeleannamine had been administered and disappearing completely 240 minutes after rectal tripeleannamine. Aerosol tripeleannamine even in the minute dose administered (six inhalations of an aerosol made from a 2 per cent solution of tripeleannamine hydrochloride) yielded complete (100 per cent) protection against the decrease in vital capacity induced by subsequently administered histamine aerosol. This protection was apparent immediately and had already begun to decrease by the end of one-half hour. Significant (40 per cent) protection lasted for approximately 160 minutes.

In the same individual no protection against the effects of histamine aerosol was apparent after the oral administration of 50 mg of diphenhydramine. When the same dose was administered rectally, 47 per cent protection was apparent one-half hour later. This level was maintained for ninety additional minutes; the protection disappeared by the end of the third hour. When 28 mg of diphenhydramine was administered intravenously, 82 per cent protection was apparent five minutes later. This level was then maintained for 180 minutes, following which the degree of protection rapidly diminished. Protection was no longer detectable four hours after intravenous diphenhydramine.

In this individual it is apparent that either diphenhydramine or tripeleannamine administered rectally is able to prevent the effects of histamine aerosol, but both are totally ineffective when given by mouth. Aerosol tripeleannamine and intravenous diphenhydramine are likewise effective.

Striking clinical relief of both asthma and hay fever followed the addition of 2 per cent tripeleannamine aerosol and of rectal tripeleannamine (50 mg two to three times daily) to the above regimen.

Case 2 (J. P.).—This housewife, aged thirty-four, was seen in September, 1948. She gave a history of perennial bronchial asthma of twenty-seven years' duration, becoming more frequent in the last five years. For the past two summer seasons, she had experienced

enced moderate hay fever, which disappeared with the first frost, and also mild atopic dermatitis of the face and left forearm. Significantly positive intradermal skin tests to dust and to mixed feathers were elicited. She had obtained no benefit from tripeleannamine, 50 mg orally, three times daily for two weeks, although this preparation produced distressing dizziness and drowsiness. Bronchodilator inhalations were effective in terminating a paroxysm, and some prophylactic relief was afforded by aminophyllin suppositories. Diphenhydramine, when given orally in moderately large doses, did not affect her hay fever or bronchospasm appreciably, even though drowsiness was produced.

After the oral administration of 50 mg of tripeleannamine hydrochloride, no alteration in the response to histamine aerosol could be detected. When 25 mg was administered rectally, however, significant (40 per cent) protection against histamine aerosol was apparent after forty-five minutes. A maximum protective level of 83 per cent appeared at the end of 120 minutes, following which the degree of protection rapidly diminished. When 25 mg of tripeleannamine hydrochloride was administered intravenously, complete protection was immediately attained. One hundred per cent protection persisted for sixty minutes, following which the degree of protection gradually lessened, falling below 40 per cent 120 minutes after the administration of tripeleannamine. Aerosol tripeleannamine was likewise potent, a peak level of 83 per cent being attained immediately after its administration. Significant (40 per cent) protection persisted for 155 minutes after the administration of aerosol tripeleannamine.

Rectal and aerosol tripeleannamine again yielded clinical relief.

Case 3 (J. Stc.).—This man, aged sixty-three, white, retired, was seen in April, 1948, and gave a three-year history of perennial asthma. Prior to being followed by the clinic, he had been digitalized for what was considered cardiac decompensation. He has been comfortably maintained on rectal aminophyllin, and obtained prompt relief of his acute paroxysms with bronchodilator aerosols. He has observed that whereas a combination of diphenhydramine and aminophyllin (Hydryllin), taken orally, afforded some relief of his nocturnal asthmatic distress, large doses of tripeleannamine alone produced neither drowsiness nor similar nocturnal relief.

After the oral administration of 50 mg of tripeleannamine, protection against the effects of intravenous histamine was entirely lacking (two trials). When the same dose of tripeleannamine was administered rectally, 67 per cent protection was apparent after thirty minutes. A peak level of 83 per cent protection was attained at 90 minutes. Significant protection persisted for an additional 150 minutes, following which the degree of protection rapidly diminished. As in previous cases, intravenous and aerosol tripeleannamine were also effective in preventing the drop in vital capacity induced by histamine. Twenty-five mg of tripeleannamine administered by vein gave immediate complete protection against the effects of intravenous histamine. The degree of protection then gradually diminished but was still significant at the end of 230 minutes. Immediately after aerosol tripeleannamine 96 per cent protection was observed. Significant protection was still present 140 minutes later, at the conclusion of this particular experiment.

In this individual, although oral tripeleannamine was ineffective, oral diphenhydramine yielded significant protecting levels. A peak of 53 per cent protection was observed 90 minutes after the administration of 50 mg of diphenhydramine by mouth. Significant protection was maintained until 210 minutes after diphenhydramine, at which time the experiment was concluded. As was the case with tripeleannamine, diphenhydramine was also active when given by other routes. When 50 mg was administered rectally, a maximum protective level of 80 per cent was attained sixty

TABLE I. THE ANTIHISTAMINIC PROTECTIVE CAPACITY OF DIPHENHYDRAMINE AND TRIPLENNAMINE IN THREE ASTHMATIC SUBJECTS WHO SHOW ABSENT PROTECTION AFTER ORAL ADMINISTRATION OF THESE AGENTS

Case	Route of Histamine	Antihistaminic Agent and Route	Peak Level of Protection (%)	Duration of Significant (40%) Protection Minutes
G. Bro.	Aerosol	Tripelennamine, oral	0	0
		rectal	100	150
		aerosol	100	160
		Diphenhydramine, oral	0	0
A. Bai.	Aerosol	rectal	47	110
		intravenous	82	210
		Tripelennamine, oral	0	0
		rectal	83	95
J. Ste.	Intravenous	aerosol	83	155
		intravenous	100	120
		Tripelennamine, oral	0	0
		rectal	83	255
		aerosol	96	140
		intravenous	100	230
		Diphenhydramine, oral	53	120
		rectal	80	195
		aerosol	77	70
		intravenous	80	180

minutes later. Significant protection persisted for 150 minutes longer, the duration of the experiment. After aerosol diphenhydramine, there was 77 per cent immediate protection against the effects of intravenous histamine; significant protection lasted seventy minutes. When 28 mg of diphenhydramine hydrochloride was given by vein, 80 per cent immediate protection was observed against the effects of intravenous histamine. The degree of protection gradually diminished; significant protection persisted for 180 minutes.

These three individuals were subjected to protection studies because of clinical indications that orally administered diphenhydramine and tripelennamine were ineffective in controlling their symptoms. For comparison we have performed similar studies on four other individuals in whom these agents exhibit the usual dramatic clinical effect. In each of these, both diphenhydramine and tripelennamine exhibited significant protection when given orally. In approximately one half of this latter group of studies, rectal administration of diphenhydramine or tripelennamine again yielded more intense and prolonged protection than followed oral administration.

The pertinent data with regard to our three cases showing absent protection after oral administration of diphenhydramine and tripelennamine are summarized in Table I. Similar data with regard to the other four patients who exhibit the anticipated protection levels are summarized in Table II.

DISCUSSION

Oral administration of antihistaminic agents in some asthmatic patients fails to produce significant protection in the laboratory against histamine-induced dyspnea and bronchospasm, which parenteral administration con-

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TABLE II. THE ANTIHISTAMINIC PROTECTIVE CAPACITY OF DIPHENHYDRAMINE AND TRIPLENNAMINE IN FOUR ASTHMATIC SUBJECTS WHO SHOW HIGH PROTECTION AFTER ORAL ADMINISTRATION OF THESE AGENTS

Case	Route of Histamine	Antihistaminic Agent and Route	Peak Level of Protection (%)	Duration of Significant (40%) Protection, Minutes
A. Nig.	Intravenous	Tripelennamine, oral	80	150
		rectal	100	210
		aerosol	60	30
		intravenous	100	300
		Diphenhydramine, oral	100	220
	Aerosol	rectal	100	285
		aerosol	0	0
		intravenous	100	210
		Tripelennamine, oral	80	200
		rectal	100	260
M. Ger.	Intravenous	aerosol	70	110
		intravenous	100	240
		Diphenhydramine, oral	74	200
		rectal	100	260
		aerosol	100	40
	Aerosol	intravenous	100	230
		oral	100	210
		rectal	100	195
		aerosol	100	75
		intravenous	70	180
W. Hun.	Aerosol	Tripelennamine, oral	70	230
		rectal	100	170
		aerosol	88	60
		intravenous	100	285
		Diphenhydramine, oral	100	170
	Intravenous	rectal	100	175
		aerosol	100	100
		intravenous	100	310
		Tripelennamine, oral	46	20
		rectal	72	210
P. Del.	Intravenous	aerosol	82	150
		intravenous	85	150
		Diphenhydramine, oral	65	170
	Aerosol	rectal	90	255
		aerosol	70	40
		intravenous	100	240

sistently affords. In other individuals, oral administration yields protective capacities similar to those found after intravenous or rectal administration.

At the present time, we can only speculate upon the cause of this phenomenon. One might be dealing with lack of gastric or duodenal absorption, with enzymatic digestion, or with hepatic inactivation of these agents. The last possibility seems most probable, since the only common factor in the other, efficient routes of administration, is the by-passing of the portal circulation. McGavack,⁴ Arbesman¹ and Serafini⁷ have also commented on the variability of "absorption rates" in man of antihistaminic drugs, the former employing blood level determinations, and the latter using histamine and antigen-antibody skin reactions.

We agree with McGavack⁴ that there is an apparent dissociation between the antihistaminic effects and the side reactions of these compounds. This was particularly exemplified by the occurrence of drowsiness in Cases 1 and 2, following the ingestion of diphenhydramine or tripelennamine, at a time when no protection was being afforded.

SUMMARY

In three asthmatic patients, orally administered tripelennamine and/or diphenhydramine were ineffective in preventing histamine-induced dyspnea and bronchospasm. In these patients, the same drugs were quite effective after rectal, intravenous, or aerosol administration. The mechanism of this phenomenon is unknown, but it may represent hepatic inactivation. The sedative effect of these agents may persist in the absence of any appreciable antihistaminic effect.

These observations in the laboratory suggest the employment of rectal, aerosol and intravenous antihistaminic agents in the clinical management of patients with hay fever and bronchial asthma who do not respond to these agents when administered orally.

370 Commonwealth Avenue

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ALLERGY SECTION AT MINNESOTA MEDICAL MEETING

The American College of Allergists, by invitation from the Minnesota State Medical Association, conducted a half-day special session June 13 at Duluth, Minnesota. An introductory talk was given by Fred W. Wittich, M.D., followed by a paper entitled "Skin Allergy, Newer Trends in Diagnosis and Management" by Stephan Epstein, Marshfield Clinic, Marshfield, Wisconsin, and Clinical Associate, Professor of Dermatology, University of Minnesota. "Respiratory Allergy; Hay Fever--Including Nonspecific and Specific Therapy" was presented by George Loomis, M.D., Winona, and Fred W. Wittich, M.D., Minneapolis. "Allergic Rhinitis and Bronchial Asthma" was prepared by Albert V. Stoesser and Lloyd S. Nelson of the University of Minnesota. The concluding paper was "Status Asthmaticus" by William S. Eisenstadt of Minneapolis.

THE PRECIPITATION OF REAGIN AND THERMOSTABLE (BLOCKING) ANTIBODY WITH AMMONIUM SULPHATE IN RAGWEED-SENSITIVE SERUM

I. Technique

D. EDWARD FRANK, M.D., F.A.C.A.

Sun Valley, California

COOKE³ *et al* demonstrated the production of another antibody in the sera of ragweed-sensitive patients after the injection of ragweed antigen. Loveless⁷ further elaborated on its inhibiting or blocking character and its thermostability compared to reagin. Frank and Gelfand⁴ enlarged on its specificity and non-existence in other immune sera. Hampton⁵ *et al*, by using a ragweed-antiragweed rabbit serum system, were able to obtain increased precipitation due to human thermostable antibody.

The general concept of blocking antibody is well accepted. Weiner⁹ defines the immune state as one in which a large amount of blocking antibody, due to the introduction of antigen, is present in the body fluids. On the opposite side, Bronfenbrenner¹ questions that reagin and blocking antibody are two distinct antibodies. Among others, he cites the work of Kleczkowski⁶ to support this view. The latter, using tobacco mosaic virus and tomato bushy stunt virus as antigens and the agglutination test, attempts to show that the heating of the antibody alone did not produce blocking antibodies, but that the heating of the euglobulin antibody containing fraction in the presence of other proteins such as albumin, or as in whole serum, produces a protein complex which is in effect the blocking antibody. The author accepted the challenge of determining whether Kleczkowski's illuminating work supporting the unitarian theory could be duplicated on the sera of untreated and treated ragweed-sensitive patients.

This first paper deals primarily with the techniques used to obtain suitable euglobulin and other antibody containing fractions.

MATERIALS

The serum from a ragweed-sensitive patient who had received ragweed extract injections previously but not for the past six years, and whose serum contained both reagin and thermostable antibody, was the source from which all the preliminary fractions were precipitated. Pooled sera from non-treated ragweed-sensitive patients was the reservoir of reagin for thermostable antibody titrations. Saturated, two-thirds- and one-third-saturated ammonium sulphate solutions were used for precipitating and washing the various fractions. Mixed ragweed extract, measured in protein nitrogen units, was used for testing. Merthiolate 1-7,500 was the preservative in some sera. A Swinney Seitz filter adapter offered a convenient means for Seitz filtration in others.

¹ Presented before the Sixth Annual Meeting of the American College of Allergists, St. Louis, Missouri, January 15-18, 1950.

METHOD

The essential method tried is that of Kleczkowski, who precipitated euglobulin by one-third saturation of the serum with ammonium sulphate, filtering the precipitate, washing the same with one-third-saturated ammonium sulphate, dissolving the precipitate on the filter paper in water, and dialyzing the solution. The insoluble euglobulin in the dialysis bag after dialysis was filtered off, and only the soluble globulin in the filtrate was used for agglutination tests. Attempts to duplicate this technique exactly in ragweed-sensitive serum encountered difficulties in obtaining an antibody-containing fraction. Several variations of the method were tried. Essentially, they consisted of trials with a protein fraction at either a 28 per cent, 33 per cent, 43 per cent or 50 per cent ammonium sulphate saturation of the serum. Ammonium sulphate in proper strength and amount was added to 1 to 5 cc aliquots of serum, directly (whether slowly or rapidly did not seem to influence the final antibody content). The precipitates were at first filtered but later centrifuged at 4,500 RPM for thirty minutes. The filtration method required large quantities of diluent to insure dissolving the precipitate on the filter paper. These dilute solutions after dialysis were devoid of antibodies. Dialysis was carried out at first against water alone. Later saline was tried, but was replaced by running tap water for two to twelve hours followed by saline. As in the work of McKhann and Chu⁸ it was found that water dialysis alone gave large quantities of insoluble euglobulin in the dialysis bag and a pH about 4; and frequently antibodies could not be detected. Originally, merthiolate was added for preservative. Later the end product was Seitz filtered.

RESULTS

The results obtained may be briefly stated, and are readily visible in the accompanying table. The percentage yields were not constant for the various fractions, evidenced by the variability (within limits) of the protein percentages obtained. The water dialysis tended to give a lower yield than water plus saline dialysis. Where reagin was present in a fraction it existed quantitatively, when tested, in approximately the same amount, regardless of the method of preparation of the fraction. Whenever reagin was present, if thermostable antibody was tested for, it was present, and again quantitatively, in constant amounts, regardless of the nature of preparation of the fraction. Dilution of redissolved precipitate before dialysis seemed to result in loss of antibody content; conversely, dilution after dialysis did not affect antibody content.

DISCUSSION

Kleczkowski states, "antibodies . . . heated with euglobulin fractions of the antisera only . . . can still unite with and flocculate their antigens

PRECIPITATION OF REAGIN—FRANK

METHOD OF PREPARATION, PROTEIN YIELD, TEST FOR ANTIBODIES (REAGIN AND THERMOSATABLE)
IN RAGWEED SENSITIVE SERUM PRECIPITATED WITH $(\text{NH}_4)_2\text{SO}_4$

Sample	$(\text{NH}_4)_2\text{SO}_4$ Saturation	Filtered	Centri- fuged	Dialysis	H ₂ O	Saline	H ₂ O plus Saline	Protein Insoluble Euglobulin	Grams/100 cc	Reagin Present Titre	Antibodies	Thermo- stable Titre	Methio- Ine Titre	Seitz Filtered	
F1	33°C*	X	—	—	—	X	—	.375	—	1-10	none	none	X	—	
F20a*	33°C	X	—	—	—	—	—	—	1.13	1-10	none	none	X	X	
F20b*	33°C	X	—	—	—	—	—	—	1.38	1-10	none	none	X	X	
F21*	33°C	X	—	—	—	—	—	X2**	.19	.61	1-10	none	X	X	
F22*	33°C	X	—	—	—	—	—	X2**	—	—	1-5	—	—	—	
F3	33°C	X	—	—	—	—	—	—	—	—	—	—	—	—	
F4	33°C	X	—	—	—	—	—	—	—	—	—	—	—	—	
F5	33°C	X	—	—	—	—	—	—	—	—	—	—	—	—	
F11	33°C	X	—	—	—	—	—	X12**	—	—	1-1	none	X	X	
F12	50°C	X	—	—	—	—	—	X12**	—	—	1-1	none	X	X	
F17	33°C	X	—	—	—	—	—	X7**	—	—	1-1	600PNU	400PNU	X	
F18*	33°C	X	—	—	—	—	—	X3**	—	—	1-4	600PNU	400PNU	X	
F19a	33°C	X	—	—	—	—	—	X9**	—	—	1.72	600PNU	400PNU	X	
F8a	28°C	X	—	—	—	—	—	Not Dialyzed	—	—	1:1	none	X	—	
F8b	50°C	X	—	—	—	—	—	Not Dialyzed	—	—	1:1	yes	X	—	
F8c	50°C	X	—	—	—	—	—	Not Dialyzed	—	—	1:1	yes	X	—	
F9	50°C	X	—	—	—	—	—	Not Dialyzed	—	—	1:10	yes	X	—	
F9b	13°C	X	—	—	—	—	—	Not Dialyzed	X12**	—	—	1:10	yes	X	—
F9c	50°C	X	—	—	—	—	—	Not Dialyzed	X12**	—	—	1:10	yes	X	—
F10	13°C	X	—	—	—	—	—	Not Dialyzed	X7**	—	—	1:2	yes	X	—
F10a	50°C	X	—	—	—	—	—	Not Dialyzed	X7**	—	—	1:2	yes	X	—
F11	50°C	X	—	—	—	—	—	Not Dialyzed	X3**	—	—	1:2	yes	X	—
F12	50°C	X	—	—	—	—	—	Not Dialyzed	X3**	—	—	1:2	yes	X	—
F13	50°C	X	—	—	—	—	—	Not Dialyzed	X3**	—	—	1:2	yes	X	—
F14	50°C	X	—	—	—	—	—	Not Dialyzed	X2**	—	—	1:2	yes	X	—
F15	50°C	X	—	—	—	—	—	Not Dialyzed	X2**	—	—	1:1	600PNU	400PNU	X
F16	50°C	X	—	—	—	—	—	Not Dialyzed	X3**	—	—	1:1	600PNU	400PNU	X
F18b	33-50°C†	X	—	—	—	—	—	Not Dialyzed	X3**	—	—	5:4	600PNU	400PNU	X
F18c	50°C	X	—	—	—	—	—	Not Dialyzed	X3**	—	—	2.90	600PNU	400PNU	X
F19b	33-50°C†	X	—	—	—	—	—	Not Dialyzed	X9**	—	—	1.55	600PNU	400PNU	X
F19c	50°C	—	—	—	—	—	—	Not Dialyzed	X9**	—	—	2.24	600PNU	400PNU	X

*In these samples, the precipitate after ammonium sulphate saturation was redissolved and diluted before dialysis. All other precipitates were made, subsequently, after dialysis.

†The number after the X indicates the number of hours dialyzed against running tap water, followed by saline.

‡Fraction between 33 percent and 50 percent saturation, after 33 percent fraction has been salted out.

. . . antibodies . . . heated in presence of protein fractions other than euglobulin . . . can combine with their antigen but cannot cause flocculation . . . and can subsequently prevent the latter from being precipitated by unchanged antibody." However, as he states in his article, he filtered off the insoluble euglobulin after dialysis, and used only the soluble globulins for his tests. Cohn² *et al.*, used Tisellius' electrophoretic technique to check the globulins precipitated by various saturations of ammonium sulphate. They found that one-third saturation resulted in a precipitate, of which only about one third was euglobulin (insoluble in water), and that the rest was chiefly water soluble gamma globulin; that at 40 per cent saturation, alpha, beta and gamma globulins were present plus about one third insoluble euglobulin; whereas, at 50 per cent saturation, alpha and beta globulins were present chiefly, with about 6 per cent of insoluble euglobulins.

Cohn's observations relate to the present problem in two ways: (1) Kleczkowski, while talking about insoluble and soluble euglobulin, actually discarded the former and used a gamma globulin for his tests; (2) the results in the present paper demonstrate the presence of reagins and thermostable antibodies in the 33 per cent ammonium sulphate saturation fraction, composed chiefly of euglobulin and gamma globulin, and also in the 50 per cent fraction composed chiefly of alpha and beta globulins. Although Kleczkowski used in reality gamma soluble globulin, his theory of the effect of heating antibodies may still be valid. It will be discussed in a subsequent paper which gives results relating to that aspect of the problem.

McKhann and Chu reduced dialysis against running tap water to twelve hours, in order to reduce the insoluble euglobulin thrown out of solution. In the present instance it was impossible to keep all the euglobulin in solution after dialysis, although the amount precipitated out could be reduced markedly, by cutting water dialysis to two hours. However, subsequent tests revealed that the quantitative presence of reagin and thermostable antibody seemed to be independent of the presence of euglobulin (unless that small amount which remained in solution determined the antibody activity). Seitz filtration removed all insoluble euglobulin, without affecting antibody titre.

SUMMARY

1. Human serum known to contain ragweed reagins and the thermostable antibody was saturated with one-third and 50 per cent ammonium sulphate. The resultant precipitate was either filtered and redissolved or centrifuged and redissolved in saline. It was then dialyzed against water or saline, or both. The insoluble euglobulin precipitate which formed on dialysis was filtered off. The soluble globulins which remained were tested for reagins and thermostable antibodies.

2. Dealing with small quantities of serum, various difficulties were encountered in attempting to obtain fractions of constant protein content. Despite the variations in total protein content from different samples and different fractions, the antibody content of all was constant.

3. The one-third ammonium-sulphate-saturation fraction is composed chiefly of soluble gamma globulin after dialysis; the 50 per cent fraction is composed chiefly of alpha and beta globulins. Both fractions showed the presence of both reagins and thermostable blocking antibodies in quantitatively about the same amounts.

7949 Vineland Avenue

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INGESTION OF 1250 MG OF DEMEROL (ISONIPECAINE) WITH SUICIDAL INTENT

A Case Report

ARMAND E. COHEN, M.D.

Louisville, Kentucky

A CASE of Demerol poisoning is reported in which 1250 mg in a single dose was taken with suicidal intent. It is of interest that this quantity of the drug produced relatively mild toxic symptoms and there was a rapid recovery with no apparent sequela.

CASE REPORT

The patient, a white man, aged thirty-four, entered the Norton Memorial Hospital at 8:30 a.m., August 20, 1949, complaining of drowsiness, sweating, dryness of the mouth and nausea following the ingestion of twenty-five 50 mg Demerol tablets. He had vomited about thirty minutes after taking the drug and repeatedly thereafter.

The patient had domestic difficulties which caused him to become profoundly frustrated and depressed. At 3 a.m. in the presence of a witness, he took twenty-five 50 mg Demerol tablets.

This patient had been under my care since 1942 and had suffered from asthma and saccular bronchiectasis since 1940. In 1942 a bronchogram was made which showed bilateral bronchiectasis involving all the lobes of the lungs. The patient moved to Denver, Colorado, where he stayed from 1942 to 1945; but there was little, if any, improvement in his condition. Another bronchoscopy and bronchogram was made July 8, 1949, which showed cylindrical and saccular bronchiectasis involving all lobes bilaterally. The bronchiectasis was so extensive that it was advised that no benefit could be offered by surgery.

Aside from bronchiectasis and chronic maxillary sinusitis, the patient showed no other significant disability. Routine allergy tests were negative. Sputum examinations showed no tubercle bacilli. Sputum cultures showed Gram positive short chain streptococci. The Kahn was negative and the urine and blood counts were normal.

Treatment was entirely symptomatic. Intramuscular and aerosol penicillin, as well as sulfa drugs, were used from time to time with varying results.

Oral Demerol was used occasionally at night. The usual expectorants such as iodides, ammonium chloride, together with postural drainage, were used with fair degree of regularity. Since November, 1948, Isuprel aerosol was used with some relief of the asthma and since June 14, 1949, 7.7 grs of sulfadiazine had been given daily. On June 22, 1949, the patient was seen at the office. He had gained weight and was feeling well. On August 18, a prescription was requested for twenty-five Demerol tablets; and, since the patient lived out of the city, this amount was sent to him on prescription from a local druggist.

On physical examination upon admission to the hospital, the patient seemed drowsy and confused. He perspired freely and complained of extreme dryness of his mouth. The pupils were equal and regular and responded to light. The heart appeared normal and his breathing remarkably clear. The temperature was 99° F, pulse 100, blood pressure 108/60. The blood count showed 13,580 WBC, of which

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INGESTION OF 1250 MG OF DEMEROL—COHEN

90 per cent were neutrophiles. The urine was normal except for three to four pus cells and occasional granular cast per HPF.

On admission a gastric lavage was done and 20 mg of Benzedrine was given intramuscularly. Blood pressure determinations were made at fifteen-minute intervals for four hours, but there was remarkably little variation from the admission recording.

The following day the blood pressure was found to be 118/70. He complained of cramping pains of both thighs, and the asthmatic condition was worse than for some time. Ammonium chloride and potassium iodide were given by mouth together with aminophyllin suppositories.

He was seen by a psychiatrist, who felt that the patient was a constitutionally inadequate individual. Note was made that the patient's mother was dead and that he had in recent years developed considerable dependency upon his mother-in-law. The psychiatrist stated that since the emotional problem had been solved, no further attempt at self-destruction was anticipated. The patient was given Benzebar tablets t.i.d. in addition to the medications for his pulmonary condition. He was discharged from the hospital August 23, 1949.

DISCUSSION .

The above case suggests that Demerol has a relative-low toxicity and that it is a fairly safe drug to prescribe to patients who might deliberately or otherwise take more than a therapeutic dose. The fact that the patient vomited within an hour following the ingestion of the Demerol and vomited repeatedly thereafter until admission to the hospital of course may have prevented the absorption of the entire amount of the drug.

The United States Dispensatory (Osal-Farrar, 24th ed., page 1425) states "Administration of Demerol hydrochloride to man in doses of 50 to 150 mg at three- or four-hour intervals, as it is given clinically, produces mild circulatory or respiratory effects only occasionally. Prolonged use has resulted in no alteration of the hematopoietic system or impairment of kidney functions. Blood sugar levels are not altered. In bed patients receiving the drug by the parenteral route, dizziness is observed in approximately 22 per cent, nausea and vomiting in 4 and 8 per cent, respectively, of cases; in ambulatory patients these effects are both more frequent and more severe. Respiration and dryness of the mouth may at times be marked. Since these reactions subside if the drug is continued they are not an indication to discontinue medication. Excessive doses, as employed in abuse of the drug, may result in tremors and possibly convulsions; the latter have occurred if the dose exceeds 0.2 gm every two hours. With therapeutic doses cerebral irritation, such as tremors and unco-ordinated muscular movements, may occur in an occasional patient. . . . Demerol hydrochloride should be administered with caution, if at all, to patients with intracranial lesions."

Andrews¹ administered parenterally an initial dose of 100 mg of Demerol hydrochloride, and thereafter, for ten consecutive weeks, doses

INGESTION OF 1250 MG OF DEMEROL—COHEN

of a size and frequency chosen by the men, with limits of 300 mg per dose and a minimum interval of one and a half hours. The dosages of Demerol in the two cases cited in some detail ranged up to 3,180 mg a day in one case, and up to 2,850 mg in the other.

SUMMARY

A case is reported wherein a patient took 1250 mg of Demerol with suicidal intent. This resulted in mild toxic symptoms, and there was prompt recovery without sequela.

Demerol is a drug frequently used by allergists. Animal experimentation has shown the relative low toxicity of Demerol, but this is the first case in so far as could be found in the literature in which a human being took such a large quantity in a single dose. The relative mildness of the toxic symptoms sustained suggests that Demerol, in addition to being an efficient drug, is likewise a relatively safe drug to use in patients in whom suicidal tendencies may be suspected.

Suit 517 Brown Bldg.

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PRACTICES AVAILABLE

Any allergist of the College interested in locating in California please contact the Secretary's office, 423 La Salle Medical Building, Minneapolis 2, Minnesota, for particulars.

* * *

Any young man who would be interested in going to Texas and locating in a good-sized city to take over the practice of a Fellow of the College specializing in allergy, will please contact the Secretary of the College at once for details.

This Fellow is a member of the reserves and is expecting to be called back to regular duty in the near future. To insure that his patients receive the proper treatment in his absence, he would be willing to make an agreement to turn over his practice for a small percentage based upon the volume that it is now. Any allergist who is able to maintain it at a larger level than it is now would keep the extra revenue. He would also be willing to sell the entire practice to another allergist with the understanding that when the emergency is over, he would not locate in the same city.

SKIN REACTIONS OF SURFACE ANTIGENS AND BACTERIAL RESIDUES

M. R. LICHTENSTEIN, M.D., F.A.C.A.
Chicago, Illinois

THE following study is part of a general investigation of skin reactivity among tuberculous patients. Previous reports^{1,5} have given details of tuberculin reactivity under various conditions in tuberculosis, and pollen hypersensitivity in those patients who had both pollinosis and tuberculosis. The availability of new, and possibly improved, bacterial antigens led to this study.

METHODS AND MATERIALS

The bacterial antigens used* were surface antigens and bacterial residues of common organisms. The surface antigens (immunogens) are obtained by rapid extraction and sedimentation of living bacteria grown on solid media. They are presumed to contain the soluble specific substance (haptinic carbohydrate) and theoretically should be an improvement over the usual bacterial filtrates. The remaining bacterial bodies, after removal of the surface antigens, are suspended to make the bacterial residues. The two fractions mentioned were obtained from each of the following bacteria: (1) *N. catarrhalis*; (2) *E. coli*; (3) Friedlanders' bacilli; (4) *H. influenzae*; (5) pneumococci 1, 2, and 3; (6) *Staphylococcus albus* and *aureus*; (7) *Streptococcus hemolyticus* and non-hemolyticus. Controls from the culture media (two varieties) were available.

All patients tested had active pulmonary tuberculosis. Most of them were afebrile and ambulatory, a few (twelve) toxic and febrile (101° to 103° F.). Eleven children, ages three to eleven years, were tested with *N. catarrhalis* and *E. coli*.

The injections were intracutaneous, with a routine volume of 0.05 cc as delivered by a 1 cc tuberculin syringe with 26-gauge needle.

RESULTS

Tests of the seven immunogens and seven bacterial residue suspensions were done first on twenty ambulatory tuberculous patients. In fifteen minutes all tests showed a slight increase in the size of the wheal, with variable erythema and no pseudopods. The residues gave slightly larger reactions than the immunogens, but in each group all reactions were closely alike in size.

At eighteen to twenty-four hours the tests revealed an area of edema and induration varying in size from 0.1 cm to 2 cm in diameter, with variable surrounding erythema and no pseudopods. The staphylococcus

Doctor Lichtenstein is Chief of Medical Service, Municipal Tuberculosis Sanatorium, Chicago, Illinois.

*These materials were generously furnished by Parke, Davis & Co.

SKIN REACTIONS OF SURFACE ANTIGENS--LICHTENSTEIN

and *E. coli* materials gave the largest reactions, the pneumococcus the smallest.

The average diameter of the induration for each of the antigens at eighteen hours follows:

	<i>Immunogen</i>	<i>Suspension</i>
<i>N. catarrhalis</i>	0.5 cm	0.5 cm
<i>E. coli</i>	0.9 cm	1.1 cm
Friedlander's	0.6 cm	0.8 cm
<i>Staphylococcus</i>	1.0 cm	0.8 cm
<i>Streptococcus</i>	0.3 cm	0.3 cm
<i>H. influenzae</i>	0.6 cm	0.8 cm
Pneumococcus	0.1 cm	0.3 cm

At forty-eight hours the tests had faded, leaving a small area of induration from 0.1 cm to 0.4 cm in diameter, with almost no erythema. At sixty hours practically no reaction remained.

Following the above tests with both immunogens and residues, twenty-nine other ambulatory tuberculous patients were tested with three to six of the immunogens. The reactions were closely similar to those described above. Twelve patients with fever from 101° to 103° F. were tested with immunogens. Most of these gave reactions identical with the first group; a few who were moribund gave very small reactions.

Tests on eleven tuberculous children (age three to eleven years) with *N. catarrhalis* and *E. coli* immunogens gave reactions quantitatively and qualitatively the same as the adults.

Tests with extracts of media were uniformly negative.

DISCUSSIONS

Surface Antigens.—It was to be expected that the immunogens, if they contained specific carbohydrates in sufficient concentration, might give immediate reactions in suitable patients. No such reactions could be noted. Whether this was due to insufficient antigen or lack of proper reactivity in the patients cannot be stated. The presence of definite delayed reactions with the immunogens indicates clearly that they contain considerable quantities of antigens similar to those in the bacterial residues.

Bacterial Residues.—The reactions with these materials appears similar to those obtained with vaccines. The parallelism, both quantitatively and qualitatively, between the immunogen and bacterial residue reactions seems to indicate that both contain the same antigen or antigens.

Are the reactions specific? The fact that patients react to all of these bacterial products with but slight quantitative differences, raises the question of specificity. Are these reactions the result of earlier infections

(Continued on Page 577)

Editorial

The opinions expressed by the writers of editorials in the ANNALS do not necessarily represent the group opinion of the Board or of the College.

ALLERGIC ASPECTS OF RHEUMATISM AND ARTHRITIS

The newly established Rheumatism and Arthritis Committee of the American College of Allergists is functioning under the able leadership of Dr. George E. Rockwell. Although multiple factors enter into the production of the rheumatic and arthritic diseases, the Committee believes that the allergic aspects are sufficiently important clinically to deserve special attention. Recognizing this, the Board of Regents of the American College of Allergists has decided that the subject for next year's panel discussion will be "The Allergic Aspects of Rheumatism and Arthritis."

While there is much evidence in the literature that allergic mechanisms are responsible for many of the clinical manifestations of the rheumatic and arthritic diseases,^{8,11,14,16} leading rheumatologists have been reluctant to accept this concept, particularly as it applies to the arthritic diseases. But many rheumatologists as recently as 1948 insisted that endocrine dysfunction was in no way involved in the production of clinical manifestations of rheumatism and arthritis.⁶ Today they are on the endocrine band-wagon. Perhaps in time these rheumatologists will become more interested in allergic aspects of these diseases, since there is increasing evidence that allergic reactions are modified in a favorable direction through the use of endocrine agents, ACTH and cortisone.^{1-7,9,10,12,13}

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LETTER TO THE EDITOR

To the Editor:

The closed-minded approach to the flat contradictions in the analysis of observed food-allergic reactions is instructively illustrated in the symposium on cottonseed sensitivity printed in the January-February, 1950, issue of the ANNALS OF ALLERGY.

The symposium includes reports of the two kinds of familial sensitivity to the cottonseed allergen—the reaginic and the nonreaginic.

The reaginically sensitive cases were exclusively reported by McGrath, Loveless and Mitchell, all of whom *selected* their cases on the basis of positive *cutaneous* reactions.

The nonreaginically sensitive cases were exclusively reported by Randolph and Sisk, and indirectly by Rowe, all of whom selected their cases on the basis of *ingestion tests*, the skin-tests being *subsequently* found negative..

The former group, after proving without question, by means of the skin tests, the specific sensitivity of all their selected patients to the cottonseed allergen, could produce no clinical symptoms in any of them through ingestion of cottonseed oil.

The latter group, after proving without question, by means of the simple ingestion test, the specific sensitivity of their selected patients to cottonseed oil, could elicit no specific cutaneous reaction with the cottonseed allergen.

Each group ignores the findings of the other and Loveless urges the adoption of "the more scientific study" which she has outlined in her "general principles"—presumably referring to her quantitative estimation of the reaginic sensitivity and concentration (dosage) of the cottonseed allergen.

However, one may observe that in "scientific" study the matter of

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quality is sometimes a much more important consideration than that of quantity. All the quantitative studies of precipitin in serum sickness had failed to solve the immunologic etiology of that condition until Karelitz, using a *different technique* (Voss), proved the antibody of serum sickness to be *qualitatively* different from precipitin and so upheld the original judgment of Von Pirquet and Schick. The partizans of precipitin will not be permitted in the future literature of serum-sickness to ignore the reports of Karelitz; and I venture to predict that future students of food-allergy will give due attention to the convincing results of the ingestion-tests reported by Rowe and by Randolph and Sisk with cottonseed oil.

In fact, Loveless and her group have been misled in their study by their very disregard of the great body of evidence which has been obtained with the ingestion procedure and reported by such competent clinicians as Vaughan, Peshkin, Rinkel, Davison, Milo Meyer and others.

They all overlooked the fact that nonreaginic sensitivity to cottonseed is so uncommon that they were likely to find no such case among their reaginically sensitive patients. Not recognizing the distinction between atopic and nonreaginic allergic symptoms, Loveless failed to notice that the symptoms which she observed in her atopic patients following ingestion of cottonseed protein were *atopic* (sneezing, conjunctival itch, itching of mouth and throat, slight nausea). The relatively large doses that were required suggest that the effect was comparable to the familiar constitutional effect of overdosage of pollen extracts, plus direct contact with the alimentary mucous membrane.

Nonreaginic constitutional symptoms, on the contrary, sometimes follow the ingestion of extraordinarily minute quantities of food protein. I have reported¹ a well controlled instance of sensitivity to sugar-cane protein in whom the characteristic symptom, vertigo, was elicited by daily ingestion of 0.0000003 mg of that protein.

Hence, one need not be surprised when the presumably small quantity of protein in cottonseed oil causes *nonreaginic* allergic symptoms, as it unquestionably does.

Part of the onus of the contradictory nature of the reports must be borne by those who have observed the nonreaginic allergic reactions without realizing and pointing out their separate etiology with reference to the atopic category. These men have faithfully recorded the absence of skin-sensitizing reagins in obviously (even violently) allergic persons, yet apparently without being able to digest the logical conclusion forced by that observation.

ARTHUR F. COCA, M.D.

REFERENCE

1. Coca, A. F.: *Familial Nonreaginic Food Allergy*, 2nd Ed., Pp. 79-80. Springfield, Ill.: Charles C Thomas 1945

Progress in Allergy

ANTIHISTAMINIC AGENTS

A Review

ETHAN ALLAN BROWN, M.D., F.A.C.A.

WILFRED KRABEK, M.S.

Boston, Massachusetts

(Concluded from the May-June issue.)

PYRIBENZAMINE

Of the many papers concerned with the effect of Pyribenzamine on anaphylactic shock in guinea pigs and on various manifestations of histamine toxicity, only those of particular interest have been chosen for review. Koepf et al²⁹³ showed that 100 mg. doses given to dogs orally, daily, for one year, and two given 50 mg. daily for the same period, had no effect on general behavior. There was no evidence of kidney or liver dysfunction or granulocytopenia. Three human volunteers given 150 mg. daily for eighty days showed no changes in well-being, body weight, kidney or liver function, blood pressure, or blood picture. Five allergic individuals given 100 to 400 mg. daily for six to 275 days showed no significant changes in blood pressure. Gross and Meier²⁹¹ showed that the severity of chemosis produced, in rabbit's eye, by the application of a 10 per cent mustard oil solution was reduced by the prophylactic administration of 1 to 10 mg./kg. intravenously or subcutaneously. Antistine (5 to 10 mg.) and Phenergan (20 mg.) had similar, but lesser, effects. The vascular reactions produced by mustard oil were not alleviated while the prophylactic administration of rutin (50 to 100 mg.) inhibited the vascular reactions but was without effect upon the chemosis. In the experimental work so far reported, histamine was either injected or aerosolized. A new approach by Kellner et al,²⁹⁵ consisted of the use of subcutaneous pellets containing Pyribenzamine (500 mg.), beeswax (2.0 gm.), which protected thirteen of fourteen guinea pigs against lethal doses of histamine for seven to sixteen days.

In dogs, the administration of Witte's peptone (1 gm./kg.) is almost invariably fatal. According to Davis and Haterius,²⁹⁶ the prophylactic administration fifteen minutes previously of 2 mg./kg. atropine, or of Pyribenzamine, 10 mg./kg., protected, in the first place, five of six, and in the second, all of six dogs so treated. The blood pressure which initially fell rapidly in all animals rose faster and higher in those given Pyribenzamine than those given atropine alone, or the combination of both drugs. From this, the authors conclude that histamine apparently, and to a lesser extent, acetylcholine, are both involved in peptone shock.

The use of antihistaminic agents in the treatment of allergic conditions in animals should, perhaps, be mentioned at this point. Rawson²⁹⁷ reported that the oral administration of Pyribenzamine (25 mg.), one to four times daily to 160 dogs with eczema, urticaria, asthma, edema, conjunctivitis, resulted in excellent effects in 43 per cent, improvement in 29 per cent, and negative effects in 27 per cent. Intravenous injection of 300 to 800 mg. in sterile saline solution into eleven horses with laminitis and nine with azoturia, food allergy, bee stings and pulmonary edema, gave excellent results in fourteen, improvement in four, and no results in two. Seventeen of eighteen cows suffering from mastitis, diarrhea, ketosis, retained placenta, septic metritis, and food allergy, showed good results. In dogs, the side reactions were vom-

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iting and nervousness and in large animals, nervousness and muscular tremor, salivation and other side effects lasting ten to thirty minutes.

Because of the histamine effects of severe burns seen in humans, Gunnar and Weeks²⁹⁸ induced burn shock in twelve of fourteen rabbits, seven receiving large doses of isotonic sodium chloride solution every two hours in quantities sufficient to give the animals 1 mg./kg. of Pyribenzamine. There was no decrease in severity, the delay of onset nor inhibition or progression of the shock noted in the treated series. On the other hand, areas of erythema on the skin of rabbits produced by burns, histamine phosphate, skin wheals and intradermal injections of turpentine were, according to Weeks and Gunnar,²⁹⁹ reduced in an average of 43, 29 and 47 per cent, respectively, by prior administration of 4 mg./kg. Pyribenzamine, which caused irritability, restlessness and, if given rapidly, convulsions in the test animals.

Pyribenzamine is so widely used that its toxic reactions must be given special emphasis. According to Brown,³⁰⁰ who gave 50 mg. tablets to a group of 100 patients at four-hour intervals and ten 50 mg. tablets within twenty-four hours to another group of fifty-six patients, while the third group of 102 patients received five placebos in twenty-four hours, the occurrence of side reactions in the three groups were as follows: drowsiness, respectively, 37, 48 and 30 per cent; headache, 26, 36, and 42 per cent; nausea, 17, 23, and 8 per cent; dizziness, 24, 41 and 15 per cent; nervousness, 13, 21, and 15 per cent; oral dryness, 29, 45, and 30 per cent, and insomnia, 12, 23 and 6 per cent. It will be noted that however much the patients taking the placebo medication complained of side reactions, there is no doubt whatsoever that the patients given ten 50 mg. tablets in twenty-four hours reported the largest amount of untoward effects.

According to Wolfson,³⁰¹ a fifty-year-old male, taking Pyribenzamine for a mild dermatitis suddenly developed a painless urinary obstruction. With the discontinuation of the drug the obstruction promptly abated, a subsequent trial reproducing the symptoms. Investigations carried out on dog intestines and uterus demonstrated the presence of a spasmogenic property in Pyribenzamine and other antihistamines. It was concluded that the urinary symptoms were the result of such a property in the drug given. Dermatitis may follow Pyribenzamine ingestion. Epstein³⁰² reported on two patients; the first, responding with a pityriasis-rosacea-like reaction; and the second, with an erythematopapular dermatitis following the ingestion of Pyribenzamine, reappearing after subsequent administration of the drug. Pipes³⁰³ reported on a ten-year-old boy, who on two occasions following Pyribenzamine in the 25 mg. dose twice daily presented a coarse, scattered papular, very pruritic dermatitis within twenty-four hours, the condition progressing to vesiculation and pustulation. According to a well-controlled study by London and Moody,³⁰⁴ Pyribenzamine may cause acute urticaria. Blanton and Owens³⁰⁵ reported granulocytopenia as probably due to Pyribenzamine following eight weeks of treatment. Provocative doses were not given. A patient reported upon by Cahan et al³⁰⁶ developed a sore tongue, sore mouth and agranulocytosis following Pyribenzamine ingestion. She had, however, until one week previously received ergotrate and empirin compound. Lott, Krug and Glenn³⁰⁷ feel certain that the administration of 100 mg. of Pyribenzamine every four hours to a twenty-year-old girl resulted in acute delirium resembling a psychosis, appearing forty-eight hours after the initiation of Pyribenzamine treatment, and improving within four hours after its discontinuation, to disappear completely in twelve hours. The patient was completely normal in three days, there being no other explanation for her reaction. Ross³⁰⁸ reported on four patients, who on 75 to 100 mg. daily Pyribenzamine for two to thirty-one days complained of blurred vision, with depressed accommodation in two, refractive changes in two, and diffuse corneal edema with an increase in corneal reflexency in one. The pupillary reflexes were normal. The changes all disappeared within two weeks after the drug was discontinued. According to the Council on Pharmacy and Chemistry,³⁰⁹ Pyribenzamine

is described as useful in preventing histamine-induced smooth muscle spasm and in treating patients with urticaria or seasonal allergic rhinitis with or without bronchial asthma. It is stated that side reactions of varying severity occur in 30 per cent of the patients treated and that therefore the smallest dose of the drug which will control symptoms should be given. In the absence of side effects, 100 to 150 mg. four times daily should be given.

Pyribenzamine has been used in the treatment of a number of skin conditions, both orally and by application. When patients were given 25 to 50 mg. three to eight times daily, Baer et al³¹⁰ found that satisfactory anti-pruritic effects occurred in 10 per cent of 124 patients with itching dermatoses other than urticaria. In this latter condition, the pruritus was controlled and the clinical lesions reduced in approximately 75 per cent of the patients. In twenty-five patients, the side effects noted included drowsiness, dizziness, excitement, sweating, headache, polyuria, pyrosis, diplopia, a feeling of cold, reduction of potency, and difficulty in urination. In some cases when the dose was reduced to 12.5 to 25 mg. three times daily and gradually increased, tolerance occasionally resulted. In a second report, Sulzberger et al³¹¹ used Pyribenzamine locally in ninety patients with a variety of dermatoses, the two to five per cent cream being applied three to four times daily. Twenty-five of forty patients with atopic dermatitis were improved, with two showing a transient lessening of pruritus, while thirteen were made worse. Of eighteen patients with dermatitis eczematosa, fourteen remained the same or became worse, with two improving in the pruritus and clinically, and two showing transient improvement. Only eight of sixteen with circumscribed neurodermatitis improved, with four showing no change or deterioration, and four more being held temporarily. Three of five patients with pruritus ani or vulvae showed no improvement, two being helped for a short period of time. Nine of eleven patients with psoriasis, seborrheic dermatitis, dermatitis herpetiformis, circumscribed scleroderma, lupus erythematosus, nummular eczema or erythema multiforme, were unchanged or made worse, with two showing temporary improvement. Of the five patients in whom the untoward reactions necessitated discontinuation of the drug, two presented an allergic eczematous contact-type sensitization, while three gave evidence of systemic side effects, probably due to absorption. Frankfeldt³¹² used both oral and topical Pyribenzamine in ninety patients with pruritus ani. Of these, four patients were forced to continue the drug, one because of profound drowsiness, one because of cardiac palpitation, and two because of a generalized maculo-papular eruption. Of the others, fifty-seven experienced relief of itching, thirty-three experiencing no relief and sixteen not returning after the first visit. Eleven of those who reacted favorably to the oral medication were able to control the pruritus by local application of the 2 per cent ointment. Aaron, Peck, and Abramson³¹³ treated twenty patients with various pruritic dermatoses, with the 5 to 10 per cent solution of Pyribenzamine administered iontophoresis. The patients usually received six to ten daily treatments, each lasting five minutes, using a 4 to 10 ma. current. Ten patients obtained complete remission, and all the others experienced either relief during the course of treatment or clinical improvement. The first few treatments caused a burning sensation and increased erythema which decreased as the treatment continued. Experimentally, two hours after a 10 per cent solution of Pyribenzamine had been introduced into the skin by iontophoresis, patch tests with concentrations of turpentine, which caused vesicles, were without effect. Rogers³¹⁴ also used the 2 per cent Pyribenzamine ointment as well as the oral medication in twenty-seven patients with skin disorders. There was little or no improvement in patients with atopic dermatitis or pustular psoriasis. Either relief of itching, improvement or complete recovery was produced in patients suffering from seborrheic dermatitis, exudative discoid lichenoid chronic dermatitis, pruritus ani, nummular eczema and contact dermatitis. In several patients, flare-ups were produced

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immediately, and in one patient, an irritating effect after the drug had been used for several weeks.

Pyribenzamine has been considered in the prophylaxis and treatment of poison ivy dermatitis. Twedall and O'Connor³¹⁵ discovered that the administration of 100 mg. one hour prior to the application of an acetone extract of *Rhus toxicodendron* to the forearm, and 50 mg. at the time of application and every four hours thereafter for twenty-four hours did not affect the vesiculation of any of five allergic subjects. One patient reported some relief of the burning and itching. In a series of 280 patients with allergic and other pruritic dermatoses, Kesten³¹⁶ observed that oral doses of 50 to 100 mg. four times daily achieved complete relief of symptoms in only forty-seven. These included six of eight patients with serum sickness, one of four with dermographism, and thirty of 166 with urticaria. In 144 patients there was a suppressive action, but in thirty-six patients, untoward reactions, including nervousness, gastrointestinal disturbances, palpitations and drowsiness, necessitated the discontinuation of the drug.

According to Silverman,³¹⁷ Pyribenzamine completely relieved the pruritus due to chickenpox and measles. The author reports that after two to three doses there is complete relief and the number of secondary skin infections is materially, if not entirely, reduced as a result of Pyribenzamine therapy.

In a carefully controlled study, Zondek and Bromberg³¹⁸ used Pyribenzamine inunctions for pruritus vulvae. The patients, sensitive to endogenous hormones, had not responded to oral administration of the drug. In order that the interpretation of the effects of Pyribenzamine might be accurate, each of fourteen patients was first treated by local application of full strength glycerine for one week and by inunctions of 3 per cent procaine in glycerine for a second week. During the third week, the solution of Pyribenzamine and glycerine was applied at eight-hour intervals. In three of the patients, allergy to endogenous hormones was the etiological factor; in four there was a vitamin deficiency, in two diabetes mellitus, trichomonas vaginitis in two, vulval vaginal mycosis in one, psychoneurosis in one, and menopausal changes in one. Of these, temporary relief of itching was obtained in seven patients, with six improving and one not responding. The relief and improvement were observed in the cases due to allergy, diabetes, vitamin deficiency and vulval-vaginal infections. The effect did not persist beyond the cessation of treatment.

The use of Pyribenzamine interchangeably with Benadryl in the treatment of penicillin sensitivity has been described in the section dealing with the latter drug. In the treatment of sensitivity to streptomycin, Cohen and Glinsky³¹⁹ gave Pyribenzamine to six of fifty-five patients with a generalized maculopapular erythematous rash with mild or extreme pruritus and eosinophilia due to streptomycin (2 gm. daily). The pruritus responded promptly, the rash being self-limiting and lasting five to ten days. Urticaria, when present, did not disappear until six weeks after the streptomycin therapy had been stopped. An exfoliative dermatitis which developed on the fortieth day of treatment in one patient following a rash which appeared on the twenty-sixth day was not relieved by antihistaminic agents and necessitated streptomycin withdrawal. The rash appeared in one of sixteen patients treated with 1 gr. of streptomycin daily and in two of sixty-six treated with 0.5 gm. daily.

In chloromycetin sensitivity as manifested by a giant urticaria, Pyribenzamine may lessen the symptoms and decrease the itching in about two hours, as demonstrated by a patient described by Sachs.³²⁰ There was no history of allergic reactions to drugs or any other type of allergy. Chloromycetin was administered in a total dose of 9 gm. over a five-day period for symptoms of typhoid fever. Seventeen days later, a second course of chloromycetin therapy was instituted, and in eight days the patient responded with erythematous patches, which in twenty-four hours were accompanied by swelling of the eyelids, hands and ankles, as well as a sore throat, extending over the trunks, arms, buttocks, thighs and hands.

The use of Pyribenzamine in intravenous pyelography was described by Getzoff,³²¹ who administered the drug before injecting Diodrast. No reactions occurred in fifty non-allergic patients so treated, with general sensitivity reactions occurring in only four of twenty-two allergic individuals. The patients received Pyribenzamine (100 mg.) and also epinephrine.

In the treatment of allergic conditions, the following results were reported by Friedlaender and Friedlaender.³²² In 200 patients treated with 50 to 200 mg. orally, children taking 25 to 50 mg., both four times daily, the drug caused partial or complete relief of symptoms in approximately two-thirds of the patients in each of the following categories: vasomotor rhinitis, 108; grass and ragweed hay fever, ninety-eight; urticaria and angioneurotic edema, twenty-four; atopic and contact dermatitis, twelve. It relieved the pruritus associated with other conditions and controlled the symptoms arising out of skin tests and desensitization treatment. It gave no relief in 30 patients with non-seasonal bronchial asthma. In 27 per cent of the cases there were side effects, the most common being gastrointestinal symptoms, drowsiness and vertigo. In the group studied by Arbesman et al³²³ there were 495 patients suffering from 565 allergic conditions, in whom relief was obtained in 411. The dose for children was 50 to 200 mg. and that for adults, 100 to 400 mg. daily. Relief was apparent in fifteen to twenty minutes and lasted for one to twelve hours. No relief was seen in patients with migraine, histamine cephalgia, Ménière's syndrome, dermatitis venenata, psoriasis or acne rosacea. The report differs from that previously given in that six of twelve patients with bronchial asthma due to grasses were reported as relieved and twenty-eight of sixty-two patients with extrinsic bronchial asthma. Very definite relief of symptoms was seen in thirty of thirty-four patients with allergic rhinitis, in eighty-nine of 106 patients with ragweed pollen hay fever, and 100 of 138 patients with extrinsic non-seasonal allergic rhinitis; in seventeen of thirty-five patients with intrinsic allergic rhinitis and in forty-four of forty-seven patients with acute urticaria. All of twenty-three patients with chronic urticaria following penicillin therapy were relieved in three days to three weeks. The conjoint studies of the Committee on Pharmaceuticals and Medicaments (American Academy of Allergy)³²⁴ listed the drug as improving 59 per cent of 277 patients with non-seasonal vasomotor rhinitis, 54 per cent of 104 patients with seasonal vasomotor rhinitis, 31 per cent of 211 patients with non-seasonal asthma, and 45 per cent of eleven patients with seasonal asthma. It also improved 77 per cent of 121 patients with acute urticaria, 78 per cent of ninety-seven patients with chronic urticaria, 78 per cent of twenty-three patients with dermographism, 57 per cent of twenty-one patients with pruritus, twenty-two per cent of nine patients with eczema, 60 per cent of five patients with histamine headache, 51 per cent of fifty-nine patients with atopic dermatitis, 20 per cent of five patients with eczematous dermatitis, 57 per cent of seven patients with unclassified dermatitis, 20 per cent of five patients with Ménière's syndrome, 28 per cent of seven patients with gastrointestinal allergy; 40 per cent of five patients with cold allergy; 1 per cent of three patients with visual disturbances; and 17 per cent of six patients with migraine. Of 978 patients treated, side effects were noted in 168, with sleepiness affecting sixty-one; nausea, twenty-six; dizziness, seventeen; headache, twelve. Other side effects listed included flushing of the skin, tachycardia, wakeful excitement, difficulty in accommodation, weakness, chills, urticaria, vomiting, early menses, dry mouth, nervousness, paresthesias, gastrointestinal cramps, and symptoms of diabetes insipidus.

Feinberg and Friedlaender³²⁵ studied 503 patients whose conditions included chronic and acute urticaria, atopic dermatitis, dermographism, penicillin and sulfonamide reactions, pruritus vulvae, chronic allergic rhinitis, seasonal hay fever, asthma, chronic headache, and gastrointestinal allergy. Twenty-one of twenty-seven with chronic urticaria and angioneurotic edema experienced relief from itching and reduc-

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tion in lesions as long as the drug was continued. In other conditions, 50 mg. doses led to symptomatic relief for several hours in most cases. The symptoms of the usual course and duration returned when the drug was discontinued. The side reactions listed above were noted.

In a comparative study, Arbesman et al³²⁶ found that 72 per cent of fifty-four hay fever patients, and 41 per cent of twenty-six asthmatic patients were relieved of their ragweed pollen sensitivities when Pyribenzamine was given alone. Another group of twenty-seven patients with hay fever and eighteen with asthma received pre-seasonal desensitization, reporting 67 per cent relief for the first group; and 56 per cent for the second. A third group of 242 patients were desensitized and given Pyribenzamine, those with hay fever reporting 95 per cent relief. The patients took 400 mg. daily and the maximum doses of pollen extract which could be tolerated. On the other hand, Fuchs et al³²⁷ reported that there was no statistically significant difference in the relief afforded hay fever patients by treatment with ragweed pollen extracts, Pyribenzamine, or the combination. The drug was given alone to a group of forty patients, 50 mg. doses three times daily, and to thirty-two patients, twenty minutes before each pollen injection. In a forty-two-day period, 65 per cent of those receiving Pyribenzamine alone, 75 per cent of those receiving pollen extract alone, and 72.6 per cent of those given both showed no or slight signs of symptoms. In 17 per cent there were complaints of the usual side reactions. Gorin³²⁸ reported on Pyribenzamine alone in the treatment of hay fever of at least three years' duration in thirty-eight children, given 25 mg. three times daily. Six were definitely improved, seven moderately improved and twelve obtained no relief. Discontinuation of the medication in the group improved caused the prompt return of symptoms. In one child, extreme drowsiness was noted. According to Henderson and Rose,³²⁹ the most favorable results following the use of Pyribenzamine occurred in the cases of hay fever, forty-one of sixty-one treated cases being kept free of symptoms. In twenty-two cases, patients with hay fever and bronchial asthma, the drug controlled the hay fever in fourteen and was not effective in the remaining eight. Ten patients were relieved of their asthma, while twelve more were not affected. In fifteen cases of chronic bronchial asthma associated with infection, relief occurred in three, but actual exacerbation of symptoms occurred in three others. In two patients, mild attacks of asthma could be aborted but severe attacks were unaffected. There was some relief in thirteen of twenty-one patients with non-seasonal allergic rhinitis. Patients who were also given a choice of Antistine and Benadryl preferred Pyribenzamine by a large majority.

The use of Pyribenzamine (0.5 per cent solution) applied topically was studied by Schwartz and Leibowitz³³⁰ in fifty-nine seasonal and thirty-five non-seasonal hay fever patients, with partial or complete relief occurring in 83 per cent of the seasonal and 75 per cent of the non-seasonal patients. Of these, 45 per cent complained of slight, and two of extreme burning sensations, 20 per cent obtaining no relief whatsoever. According to Brem and Zonis,³³¹ however, the application of 0.5 per cent solution locally brought about successful antihistaminic and local anesthetic effects in seventy-six of eighty-one patients with allergic rhinitis, with only two patients being unable to tolerate the drug because of aggravation of allergic symptoms and head pain. In some patients there was transitory stinging of the otopharynx, and mild paroxysms of sneezing. Relief usually lasted one to twenty-four hours.

The application of an aerosol of Pyribenzamine (2 per cent) solution was studied by Feinberg and Bernstein,³³² who reported that its use every two to three hours benefited twenty-seven of thirty-four patients with nasal congestion due to seasonal hay fever or allergic rhinitis. Only those patients who could not obtain results or tolerate oral antihistaminic therapy were treated. The effects of the solution were

frequently not observed until after several applications. Of fifty-seven patients with moderate bronchial asthma, most of whom had not responded to oral medication, ten were effectively relieved and seventeen slightly so. Patients with spasmodic cough without dyspnea responded better than those with true asthma. Twelve of sixteen patients reacted favorably. Although less effective than aerosol epinephrine solutions, the Pyribenzamine solution was considered to be less toxic.

Nasal iontophoresis with Pyribenzamine has been reported upon by Fenton and Huffman,³³³ who treated patients with seasonal and perennial hay fever twice weekly (3 to 7 ma. for 8 minutes each nostril) using nasal packs saturated with 2 to 5 per cent solutions. Temporary dizziness occurred in 50 per cent and drowsiness in 20 per cent of twenty patients, in whom immediate improvement was obtained in eight, with two being relieved for eight hours and six for forty-eight hours. In addition, eleven patients with perennial hay fever were treated for four to eight weeks and showed 75 per cent benefit in five subjects, in two of whom relapses occurred in two weeks. Moderate improvement of fairly long duration occurred in the other six. In five patients, in whom other forms of antihistaminic therapy had failed, Aaron³³⁴ found that iontophoresis with Pyribenzamine (5 per cent aqueous) brought relief for one to four days. Of two additional patients with allergic perennial rhinitis, one obtained relief for more than seven days, but another for only three hours. One with vasomotor coryza complained of dryness of the nose lasting one day.

As with the other drugs reviewed, Pyribenzamine has been used for a number of miscellaneous conditions. Since these may in time prove to be more important than perhaps those due to allergy, they are, as a matter of record, listed. According to Foster and Hanrahan,³³⁵ a homograft in a Negro female with a full thickness skin defect appeared to be viable at the end of sixty and ninety days. Although it was not possible to ascertain whether the original graft had been replaced by tissues from the host, nevertheless, it is felt that the administration of Pyribenzamine for homografting may have been responsible for the successful result.

Moseley³³⁶ used Pyribenzamine (1 per cent aqueous) in two portions of 10 c.c. each as a mouth wash and gargle to provide oral and pharyngeal anesthesia for thirty patients prior to gastroscopy. The drug diminished the gag reflex and permitted the passage of a gastric tube in five patients. A 1 per cent solution was used fifteen minutes before eating to relieve discomfort in food ingestion in two patients with aphthous stomatitis. In two patients with severe sore throats and one with painful caries, topical application relieved the condition, as it did in two patients with painful hemorrhoids, who used the drug in an ointment base. The anesthetic effect lasted one to two hours. In normal individuals, it was discovered that a mouth rinse (0.5 to 1 per cent) used for one to two minutes caused a bitter taste, which disappeared in thirty to forty-five minutes with anesthesia coming on in four and lasting up to thirty minutes.

Although the use of antihistaminics in tuberculosis has already been noted as favorable, Guy³³⁷ found no significant alteration in the skin reaction of five individuals to whom 150 mg. of Pyribenzamine was given orally one hour before, and 650 mg. in divided doses forty-eight hours after, the intracutaneous injection of 1:1000-1:100,000 old tuberculin skin tests. There was no significant alteration in the reaction. Friedman and Silverman³³⁸ found that oral doses (60 mg. daily) for four days had no inhibiting effect on the tuberculin reaction of forty-three children. In doses of 240 mg. daily for four days there was no effect on tuberculin reaction in ten children. They suggest that in the routine tuberculin testing, one need not be concerned as to whether the patient is receiving coincident Pyribenzamine or any other antihistaminic medication.

Green and Kline³³⁹ found Pyribenzamine useful in the treatment of varicose ulcer.

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In eight patients in whom the ulcers varied from 2.5 by 2.5 cm. to 10 by 10 cm., healing occurred in four to ten weeks, with pain and edema subsiding rapidly in eight patients given 200 to 500 mg. daily. The patients discontinued all local treatment, excepting a small amount of ointment and zinc stearate dusting powder. All of the patients had previously been treated unsuccessfully with ointments and two had had injection therapy. Observation of five patients four to thirteen months later showed no evidence of recurrence.

McEachern³⁴⁰ administered doses of Pyribenzamine (50 mg. three times daily) to a patient with angina pectoris who had developed contact dermatitis. The irritation was relieved in four to six hours and the drowsiness seen initially disappeared in four to five days. The patient reported that his anginal pain was alleviated and the drug was therefore continued twice daily and reduced in dosage. In seven of eight additional patients treated with Pyribenzamine, the angina pectoris was definitely reported as improved, as measured by exercise tolerance.

Hoffman³⁴¹ gave 50 mg. three times daily to forty pregnant patients, who suffered from albuminuria and/or hypertension and in all of whom salt and fluid intake had been restricted. Of these, eleven of thirteen with albuminuria became albumin-free and two were not benefited. Ten of twelve with hypertension showed a significant drop in blood pressure, with two remaining unchanged, and twelve of fifteen suffering from both conditions showed a definite drop in blood pressure, while eleven became albumin-free. In three patients neither condition was improved, one of these presenting a still-born and another, a premature infant.

According to Perry and Horton,³⁴² in twelve of fourteen patients in whom histamine caused increase in gastric acidity, Pyribenzamine given in doses of 100 to 400 mg. daily for one to eight days proved to be without effect. In histamine-induced headaches, it was considered that Pyribenzamine lessened the intensity and duration of the pain in three of four patients, in the fourth of whom no headache developed. In three patients hypersensitive to cold, both Pyribenzamine and Benadryl gave symptomatic relief, reducing the severity and duration of the urticaria and edema. Rubin and his co-workers³⁴³ noted that two patients under treatment for solar urticaria found that the areas of skin normally exposed were more tolerant to sunshine than those usually covered. The observation was confirmed by exposing the whole body surface of one patient to the irradiation of an artificial sunlamp daily with Pyribenzamine given in 50 mg. doses three times daily. Fourteen days after the drug had been discontinued, sensitivity tests to light on both exposed and unexposed parts of the abdomen showed that the irradiated portions had acquired a tolerance more than 200 times greater than the covered parts. This effect was due pigmentation and/or thickening of the horny layer. The authors feel that no immunological desensitization mechanism was involved.

Morrow³⁴⁴ preferred Pyribenzamine to Benadryl in the treatment of 241 patients with various dermatoses. Only ten to 12 per cent of those on Pyribenzamine suffered side effects, namely drowsiness, which occurred, however, in 50 to 60 per cent of the patients treated with Benadryl. Headache, nausea and diuresis occurred to an equal extent in both groups. Patients suffering from penicillin reactions, pruritus ani and vulvae, acute and chronic urticaria, erythema multiforme, poison oak dermatitis, dermatitis venenata, and dermatitis medicamentosa, as well as patients with seborrhea showed some improvement. Treatment was less successful in patients with atopic dermatitis, nummular eczema, post-scarbic pruritus, stasis dermatitis. Dermatitis herpetiformis, jaundice pruritus, neurotic excoriations and actinic dermatitis were not improved. In several patients, both drugs were given simultaneously with no added benefit.

Kells³⁴⁵ recommends Pyribenzamine as an adjunct in the control of morphine withdrawal symptoms, administering the daily requirements of morphine in six

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doses every four hours, reducing by 10 per cent each day and starting Pyribenzamine (50 mg. four times daily) when the morphine dosage is one grain. The Pyribenzamine is continued for three days after the last dose and is needed thereafter to relieve withdrawal symptoms. No sedation is used excepting sodium bromide. The author believes that Pyribenzamine neutralizes an anti-morphine substance responsible for abstinence symptoms.

Sherry³⁴⁶ found that in five patients with Hodgkin's disease, who responded to nitrogen mustard, the fever and glandular enlargement responded excellently to six daily doses of Pyribenzamine. A patient who suffered a second flare-up after a course in nitrogen mustard responded similarly to the drug.

According to Murray,³⁴⁷ Pyribenzamine will cure the common cold as observed in 397 and 494 patients treated with Pyribenzamine every four hours. Some patients reported relief after the first two tablets, and 110 had no symptoms after forty-eight hours. In 204 patients, the cold disappeared in one to three days, and in eighty-three, the cold was greatly improved. Only seven patients lost time from work because of colds; twenty-two of ninety-seven patients who did not respond to treatment suffered untoward reactions, dizziness affecting seven, drowsiness, six, severe headache, five, and digestive disturbances, four.

Schiller and Lowell³⁴⁸ discovered that Pyribenzamine did not influence the pulmonary response to inhaled extract of pollens, as measured by change in vital capacity in three asthmatic individuals. They feel, therefore, that neither acetylcholine nor histamine are determining factors in the production of pollen-induced asthmatic attacks.

PYRROLAZOTE

Vander Brook et al³⁴⁹ reported that Pyrrolazote showed the same degree of antihistaminic activity on isolated smooth muscle as did Pyribenzamine, but was active seven times as long. In the usual guinea pig, dog and cat tests, the acute toxicity of Pyrrolazote was about one-half that of Pyribenzamine when given intravenously. Chronic toxicity studies in rats shows that a dose of 10 mg./kg. orally, five days each week for ten weeks, was harmless. Very large doses caused degenerative fatty infiltration of the liver.

The clinical studies by Ogden, Derbes and Cullick³⁵⁰ showed that patients with severe symptoms noted significant difference in relief, while those on mild or moderate symptoms reacted almost equally to both the drug and the placebo. The patients took the placebo and Pyrrolazote tablets for a week each, alternately, for varying periods of fifteen to twenty weeks, only one week's supply being dispensed, the patient noting on a form each week the time of onset of attacks, the severity of symptoms, the duration of attacks and the number of tablets taken and the frequency with which the tablets were ingested. Sixty-one per cent of forty-six patients suffered from bronchial asthma. The severely affected patients demonstrated 10.55 hours of severe symptoms each week while on the placebo tablets in comparison with 5.08 hours of severe symptoms each week while taking Pyrrolazote. For total symptoms, mild, moderate and severe, there was an average of nineteen hours while taking the placebo, as compared to twelve hours while taking the drug. No patient knew when he was taking a placebo or the drug tablets. The authors note that side reactions are easily subject to false interpretation, since patients are frequently warned of their possibility and, if they have experienced them while on the drug, they are quite apt to complain when taking the placebo. Mild drowsiness was a complaint on thirty occasions with the drug and on twenty-one with the placebo, with severe drowsiness by one patient taking either. Nausea was experienced by thirteen patients on Pyrrolazote, and nine on the placebo. No patient complained of severe nausea while taking the drug, but one of such nausea on the placebo. Vomiting occurred respectively in six patients on Pyrrolazote and four on the placebo. Headache occurred in eighteen and twelve respectively and palpitations in one and none, respectively.

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Eight patients had no side reactions with Pyrrolazote and eighteen on the placebo. The authors conclude that Pyrrolazote is a potent antihistaminic agent which compares favorably with other similar preparations. Work is in progress with a two-stage tablet made up with 25 mg. of the drug in the outer coat, with 25 mg. present in an inner ileosol-coated tablet.

THENFADIL (WIN 2848)

Thenfadil is a relative newcomer to the field. The pharmacological properties have been reported by Hoppe et al³⁵¹ who show it to be significantly more toxic than structurally similar antihistaminic agents. It would appear that of the bromo and chloro analogues, the first is approximately equal to, and the second less active than, Pyribenzamine. The laboratory studies indicate that the drug itself is approximately twice as active as Pyribenzamine. In a second communication, Hoppe and Lands³⁵² demonstrate that the average acute toxicity is 10 per cent greater than Pyribenzamine when given intravenously; 30 to 100 per cent greater when given subcutaneously and intraperitoneally in mice; and 30 per cent greater given orally in mice. It is 30 per cent less toxic than Benadryl given orally in mice. The drowsiness in mice was measured by the mean waking time from sleep induced by 100 mg./kg. of Evipal and was discovered to be prolonged 8 per cent by Thenfadil, 11 per cent by Pyribenzamine, and 43 per cent by Benadryl, each given in doses of 10 mg./kg. subcutaneously.

Studies in human subjects by Luduena and Ananenko³⁵³ showed that in twenty-three the wheal induced by histamine (1 to 2 per cent) solution applied to the skin was inhibited or controlled by the application of Thenfadil (5 per cent) to the same area; if given before histamine, the effects were aborted. The clinical evaluation of Thenfadil will probably be available in the near future.

THEPHORIN

The pharmacological properties of Thephorin have been studied by Lehmann³⁵⁴ and also by Lehmann and Stefko.³⁵⁵ The usual protection to histamine aerosol was measured, the acute toxicity of Thephorin by various routes of administration being tabulated. Worthy of note, however, is the action of Thephorin on histamine-induced gastric secretion in dogs and on gastric ulcer formation in rats. The anti-ulcer effect of Thephorin is "striking." The evidence available suggests that the effect may be considered as a chemical vagotomy. In the same animals, atropine was ineffective, while Thephorin reduced histamine-induced gastric secretion in dogs with Heidenhain pouches by about 30 per cent. The effects in cats, rabbits, dogs and guinea pigs were later reported upon by Lehmann and his colleagues³⁵⁶ in a third detailed and well-controlled series of experiments.

The tolerance studies for Thephorin by Boyd et al,³⁵⁷ using 100 normal subjects varying in age from seventeen to seventy-nine years and given doses of 75 to 600 mg. Thephorin orally daily for at least one week, showed dehydration of the mucous membranes to occur in 22 per cent and insomnia in 21 per cent. In all, forty-two subjects developed one or more toxic symptoms. In five subjects taking 300 mg. daily, the drug had to be stopped because of the severity of the side reactions, but in other subjects taking Thephorin for one month there were no significant changes in the electrocardiogram, the non-protein nitrogen of the blood, the peripheral blood count, or the urine. The drug is generally less toxic, weight for weight in daily doses of 150 to 600 mg., than are Benadryl or Pyribenzamine.

Used topically by Ellis and Bundick³⁵⁸ a 5 per cent Thephorin ointment in a carbowax base or a 5 per cent lotion for twenty-eight to sixty-eight days in fifty patients gave good results in thirteen, fair in thirteen and poor in twenty-four. In fourteen patients, the eruption became worse and tended to spread, and five of these

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patients reacted positively to patch tests with the ointment. Three of five patients reacted to the lotion. The other nine could not be tested because of the aggravated skin lesions. According to Laymon, Madden and Schmid,³⁵⁹ patch tests on 324 patients with dermatoses who had used Thephorin in the 5 per cent standard ointment for one week to ten months showed a positive patch test to two women with neurodermatitis, and one man and two women with contact dermatitis, pruritus vulvae and atopic dermatitis. A number of reactions to the base were seen, these patients giving negative reactions to the solution.

In 1948, Wooldridge and Joseph³⁶⁰ reported that neurodermatitis was completely cured in two of twenty-three patients, and more than 50 per cent improved in fifteen patients following therapy with Thephorin. Three patients were not benefited and one became worse. All of the patients took the oral medication, except two who were treated only with the ointment. Some of the patients, who were infants, received 15 to 20 mg. daily, with four infants responding with irritability and sleeplessness. The authors summarized their work saying that seventeen of the twenty-three patients showed more than 50 per cent clearing of the condition, seven over 75 per cent clearing, and eight between 50 and 75 per cent. Two patients were helped slightly, three unchanged and one became worse. Two, as noted above, were cured. In a second report³⁶¹ the authors listed nineteen of twenty-three patients suffering from disseminated neurodermatitis relieved and nine of fourteen patients from circumscribed neurodermatitis. The ointment was applied three times daily and massaged into the skin. Of the seventeen patients with circumscribed neurodermatitis, fourteen were treated while three served as controls. Of these fourteen, three had a high initial improvement with a relapse later; five had 100 per cent improvement subjectively but 50 per cent or less objectively, while four had more than 75 per cent improvement subjectively and 50 to 75 per cent objectively, while two patients had less than 50 per cent improvement subjectively and none objectively. The three control patients given the ointment base showed no improvement whatsoever. Side reactions were infrequent and one patient showed a positive reaction to patch tests.

Laymon and Schmid³⁶² continued their work with Thephorin and reported that pruritus was adequately relieved in 80 per cent of fifty-eight patients with various dermatoses, including circumscribed disseminated neurodermatitis, eczematous eruptions, lichen planus and psoriasis and dermatophytosis, the 5 per cent carbowax ointment being used. In another group of eighteen using the 5 per cent Thephorin lotion, nine of eleven with contact dermatitis and two of three with dried lichenified plaques and all of four with neurodermatitis obtained relief of their pruritus.

In dermatoses characterized by wheal formation, Kesten and Sheard³⁶³ found the ingestion of Thephorin (50 mg.) gave relief to thirty-three of forty-one patients and also stopped the pruritus in twenty-two of thirty-nine with intensely pruritic dermatitis. In twenty-one patients, however, treatment was discontinued because of side effects which in order of frequency included: nausea, anorexia, headache, drowsiness, palpitations, restlessness, depression, vomiting, indigestion, and increase of itching and dizziness.

The most recent report by D'Avanzo³⁶⁴ proved the contradictory nature of such clinical studies. The author treated seventy-four cases of pruritic dermatoses, twenty-four of whom suffered from disseminated neurodermatitis most of whom did poorly, eight only showing an initial slight-to-fair improvement, with six refractory and two becoming sensitized to the ointment, the greater number of the patients becoming worse after treatment. Of twenty-six patients with circumscribed neurodermatitis, 39 per cent were very much improved with two becoming refractory; twenty-four additional patients with miscellaneous dermatoses, including a typical case of nummular eczema, improved in one-half of the group, four becoming refractory and two becoming definitely sensitized. The sensitizing index of Thephorin ointment is given at 16 per cent but should read, due to an arithmetical error, 5.4 per cent.

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Frank^{364a} used Thephorin tablets (25 mg.) and the syrup (10 mg./dram) in 140 allergic patients, who received the tablets one to three times daily, the dose being increased until the patient derived benefit from medication or until side reactions occurred. Best results were obtained in cases of non-seasonal and seasonal rhinitis. Other conditions treated include allergic conjunctivitis, urticaria, angioneurotic edema, neurodermatitis, contact dermatitis, and other miscellaneous manifestations. Side effects occurred in 38 per cent of the 140 subjects studied, but even the most severe reactions required no measures other than discontinuation of the drug. Insomnia was prevented by the concomitant administration of a mild sedative.

Bedford Shelmire^{364b} used Thephorin ointment in 305 patients with successful results in 62 per cent of twenty-nine patients with atopic dermatitis, 68 per cent success in fifty-seven patients with contact dermatitis, 91 per cent success in fifty-six patients with circumscribed neurodermatitis, 77 per cent in nine with pruritus ani or vulvae, and 76 per cent relief in miscellaneous pruritic dermatoses. The average successful percentage results were 76.4 for 305 patients.

The miscellaneous uses of Thephorin include the 5 per cent ointment as applied locally to bee stings, or to ant bite areas in eight patients by Strauss,³⁶⁵ who reports that the intense pain and stinging sensation were relieved within two minutes with no local swelling occurring. Local pin-point areas of petechial hemorrhages disappeared within seventy-two hours.

Schloss³⁶⁶ noted that of forty-one patients with 126 complaints referable to the digestive tract were relieved of sixty-nine symptoms in twenty-six patients, with twenty-six more partially relieved, Thephorin being administered thirty minutes before eating to those patients who reacted immediately after their meals, and thirty minutes after eating to those who reacted after a longer interval. The best results were obtained in the alleviation of diarrhea, nausea and abdominal pain or fullness. No note is made of ill effects.

A report by Berger³⁶⁷ showed that Thephorin relieved both the postencephalitic and idiopathic types of Parkinson's disease, doses of 25 to 50 mg. being administered two to four times daily. Six of twenty-four patients had to discontinue treatment because of side reactions, but of the remaining eighteen, thirteen responded favorably. As noted above, Thephorin and also Benadryl and Neohetramine and Pyribenzamine were used by Judd and Henderson³⁶⁸ in the treatment of primary tuberculosis, doses varying from 50 mg. three times a day initially, to doses of 500 mg. daily, the patients receiving at least ten weeks of treatment. A decrease in the coughing sputum, fever and other symptoms was noted, with a lessening of the skin tests. The best results were obtained against the acute exudative type of tuberculosis, the treatment losing its effectiveness as tuberculous lesions increased in chronicity.

By including Thephorin with hyposensitization treatment, Maietta³⁶⁹ discovered that patients could take high pollen dose levels within a short period of time, with a substantial decrease in the number of required injections. The author feels that large pollen doses conferred a "tremendous degree of protection, heretofore not always obtainable to all the patients during their specific season." Thirty-two per cent of the patients reported 100 per cent protection; twelve of fourteen co-seasonally treated patients reported 100 per cent protection, and the remaining two suffered only mild hay fever symptoms. The doses were two to three times those recommended, and side reactions to Thephorin and eight other antihistaminic agents employed were encountered in only twenty-seven patients (60 per cent) but were not sufficiently severe to warrant discontinuation of the drug.

The well-publicized paper by Brewster³⁷⁰ on Thephorin in the treatment of common colds needs only brief mention. The drug was used in 25 mg. doses at four-hour intervals, for three doses, as the only treatment in a series of 2,614 patients suffering from colds. Parallel cases were given an equal number of placebo tablets. Fifty-four per cent of the cases who were given the drug, and who started treatment within

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six hours, were cured in twenty-four hours; and 75 per cent of all cases who started within forty-eight hours were either cured or considered the treatment satisfactory. On the other hand, those who started treatment within six hours with the placebo tablet showed a 32 per cent cure. The side effects, in order of frequency, of those who took the drug were drowsiness in 12 per cent, dizziness in 6 per cent, insomnia in 6 per cent, nervousness in 3 per cent and headache in 3 per cent. Of those who received the placebo drug, 10 per cent complained of side effects. Not only were 32 per cent of the patients who took the placebo cured six hours after symptoms but 21 per cent reported improvement and 47 per cent were unimproved. After twelve hours or less, 28 per cent of the patients taking the placebo were cured, 25 per cent were improved and 47 per cent unimproved. After forty-eight hours, 26 per cent reported cure, with 29 per cent improvement and 45 per cent unimproved.

A clinical report on the use of Thephorin in allergic conditions was made by Reynolds and Horton³⁷¹ who treated sixty-two patients with various types of allergic manifestations, reporting that thirty-three obtained excellent relief and twenty-three no relief from daily oral therapy of 25 to 200 mg. Seventeen of twenty-two hay fever patients achieved excellent relief, seven of eleven patients with vasomotor rhinitis, five of six with cold allergy; one of three with acute urticaria and none of three with each, chronic urticaria and migraine. Of the patients with atypical histaminic cephalalgia, two of nine achieved excellent relief as did patients with Raynaud's disease, dermographia, and erythromelalgia. These same patients were either unaffected by, or sensitive to, Benadryl and Pyribenzamine. No serious toxic effects were seen.

In 1948, John Peters³⁷² reported on 142 patients good results being seen in sixty-six of sixty-eight with hay fever; thirty-one of thirty-four with hay fever and asthma; three of seven with bronchial asthma; all of seven with pollen asthma; eight of ten with dust vasomotor coryza; nine of ten with various types of dermatoses, one patient with sinusitis, and one with hay fever and dermatitis. Fair results were obtained in one of two patients with migraine, but side effects occurred in fifteen patients, the most frequent being gastric disturbances, insomnia, nervousness and excessive perspiration.

Cohen et al³⁷³ used the drug in 292 patients, and reported 75 to 100 per cent relief in forty-two of eighty-three patients with bronchial asthma, 105 of 161 with allergic rhinitis, thirteen of eighteen with angioneurotic edema, five of eighteen with allergic dermatitis and eight of twelve with migraine. Fifty-four patients complained of nausea and vomiting, constipation, palpitations, insomnia, headache and urticaria. Discontinuation of the drug was necessary in eleven. Patients were alternately given Thephorin and Pyribenzamine and preferred the former. Gelfand³⁷⁴ discovered that the administration of 50 to 100 mg. of the drug improved thirteen of twenty-two cases of bronchial or pollen asthma, twenty-nine of sixty-four with seasonal hay fever, eleven of twenty-nine with perennial allergic rhinitis, five of nine with acute or chronic urticaria, atopic eczema or contact dermatitis, and none of five with angioneurotic edema. Serious side effects were reported as infrequent. In the series studied by Criepp and Aaron,³⁷⁵ the drug brought complete relief to 44 per cent of 180 patients with hay fever, 35 per cent of seventy-one with allergic rhinitis, 16 per cent of seventy-one with bronchial asthma and 12 per cent of eight with contact dermatitis. It substantially helped 43 per cent of thirty cases of urticaria and angioneurotic edema. The side effects were chiefly nervousness and palpitations, nausea and vomiting or insomnia, but also drowsiness, headache, constipation and urinary symptoms occurred in 23 per cent of 389 patients. Pennypacker and Sharpless³⁷⁶ reported that with 50 mg. doses daily, thirty-one of forty patients with hay fever were helped, twenty-one markedly and ten moderately, with slight improvement in six and no effect in three. Insomnia affected fourteen; tension, nine; dizziness, grogginess,

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lassitude, urinary urgency or chilliness, five each, and gastrointestinal disturbances, one. Some patients are reported as finding the stimulation of the drug pleasant.

It should be noted that the last three reports were all published in September of 1948, as were the next three. Sternberg and Gottesman³⁷⁷ treated seventy-six patients, of whom five experienced insomnia, and one, nausea. Eighteen of forty-one patients with hay fever, nine of twenty-six with bronchial asthma, none of six with vasomotor rhinitis, two of two with urticaria, and none of one with migraine reported good results, with eleven of the seventy-six reporting fair results and the remainder negative effects. The series by McGavack et al³⁷⁸ on 136 patients showed twelve of sixty-six with hay fever, five of twenty-five with allergic rhinitis, one of twenty-four with bronchial asthma, five of sixteen with urticaria, none of two with contact dermatitis, and one with Fox-Fordyce disease, food allergy and migraine receiving complete relief. Sixty-five patients reported improvement and the remainder no effect. The results are said to be comparable to that of Benadryl in hay fever and urticaria, while the drug was less effective in vasomotor rhinitis and asthma. The toxic symptoms in order of decreasing frequency were: dryness of the mouth, insomnia, constipation, dizziness, jumpiness, burning of the conjunctivae, intestinal cramps, drowsiness, weakness and palpitation, untoward reactions occurring in twenty-two of the patients with hay fever, in seven of those with asthma and in seven with rhinitis. Paul et al³⁷⁹ reported fair to excellent results in 154 of 197 patients with hay fever, and fifty-four of seventy-one with non-seasonal vasomotor rhinitis. Fair to excellent results occurred in six of twelve patients with bronchial asthma. Of the total number of 280 patients treated, side reactions consisted of sleeplessness, nervousness, chills, nausea, headache and dryness of the mouth and throat occurring in seventy-five patients, with eleven discontinuing treatment because of severe reactions.

In the same year, and to patients undoubtedly exposed to the same type of season, Moncheck³⁸⁰ administered Thephorin to 113 patients for 168 allergic symptoms for one to 171 days. Of those with hay fever, thirty-seven of forty-eight had relief lasting several hours, as did twenty-six of forty-five patients with bronchial asthma; forty-two of sixty-one with vasomotor rhinitis; eleven of twelve with cutaneous allergies, such as acute or chronic urticaria, contact dermatitis and atopic eczema. In thirty-seven patients, the untoward reactions seen included: insomnia, irritability, drowsiness, dizziness, respiratory distress, urinary retention and nausea. Schwartz and Leibowitz³⁸¹ reported symptomatic relief in forty-six of sixty patients with hay fever, thirty-three of fifty-five with vasomotor rhinitis, three of twenty with bronchial asthma, three of four with chronic urticaria and one with contact dermatitis. Twelve of the ninety-five patients suffered side reactions, which are listed as drowsiness, dryness of the mouth, headache, indigestion, tiredness, dizziness, palpitations, or bitter taste, none being sufficiently severe to require discontinuation of medication.

In the series studied by Levin and Moss,³⁸² consisting of 109 allergic children, the drug was found effective in 81 per cent of those suffering from hay fever; 75 per cent of pollen asthma, 73 per cent of perennial asthma, 66 per cent of allergic rhinitis, 75 per cent of infantile eczema and urticaria. Reactions sufficiently severe to require discontinuation of the drug occurred in 8 per cent of the patients, with side reactions in 20 per cent of the group, the drug having a mild sedative effect in children in contrast to the stimulating effect seen in adults. Maietta³⁸³ used the drug intravenously in seventeen patients with bronchial asthma, of whom four were in status asthmaticus. It was noted that the wheeze and dyspnea lessened in one hour with the vital capacity being increased and the patients losing their epinephrine-fasciness. Migraine was relieved in two patients within a few minutes and within one hour with intramuscular Thephorin. The results in five patients with angio-neurotic edema and urticaria and two with urticaria and one with eczema and angio-neurotic edema were striking with the intravenous medication.

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TAGATHEN (CHLOROTHEN)

In a preliminary report, Taub, Miller and Taub³⁸¹ reported that Tagathen gave three to four hours relief in thirty patients with seasonal and perennial allergic rhinitis and three with urticaria, the usual dose being 100 to 200 mg. daily. An urticaria patient was given 25 mg. every two hours to a top dose of 200 mg. daily. In three patients, untoward reactions, such as drowsiness, vertigo, headache, confusion, weakness, palpitations, diarrhea and abdominal cramps appeared, with severe diarrhea necessitating discontinuation of the drug in one patient, who was also unable to tolerate other ethylenediamine-derived antihistaminic agents. One of the patients was also unable to take Pyribenzamine.

Phillips and Fishbein³⁸⁵ used Chlorothen to treat ninety-two patients with colds, the tablets (Caubren) also containing acetophenetidin and caffeine, the tablets being taken every three hours for a minimum of forty-eight hours. The average duration of colds in the series was 2.7 days, while in comparison among seventy-four patients given aspirin alone, the average duration of colds was 5.3 days. Two patients discontinued the use of the drug because of light-headedness and dizziness, while ten patients could not use aspirin because of gastrointestinal disturbances and dizziness.

TRIMETON AND CHLOR-TRIMETON

The chemical characteristics, the acute chronic toxicity studies and the antihistaminic action of Trimeton *in vitro* and *in vivo* with mice, rats and dogs, cats and guinea pigs has been the subject of a detailed report by Labelle and Tislow³⁸⁶ and by Sperber and his colleagues.^{387,388} The clinical evaluation by Brown et al³⁸⁹ on 227 patients presenting twenty allergic and non-allergic syndromes, alone and combined, shows that on 6.25 to 25 mg. one to four times daily, 61 per cent were completely symptom-free and an additional 22 per cent moderately comfortable. On those with hay fever, 90 per cent were relieved, of urticaria, 81 per cent; and with mild extrinsic bronchial asthma, 80 per cent. Side reactions, chiefly drowsiness, appeared in 16 per cent of the patients, being sufficiently mild in 9 per cent to permit the continuation of the drug and severe in only 6 per cent in whom the medication had to be discontinued. Wittich³⁹⁰ administered 25 mg. three times daily to 125 patients, reporting good and fair results in thirty-one of thirty-three with hay fever; nine of eighteen with perennial allergic rhinitis; ten of thirty-eight with bronchial asthma; nine of thirteen with urticaria; one of one with angioneurotic edema, one of four with gastrointestinal allergy, five of six with atopic dermatitis, none of two with contact dermatitis, two of two with generalized pruritus and six of seven with allergic headaches. Nausea occurred in one patient with perennial allergic rhinitis, recurring when treatment was resumed; one patient developed vertigo and abdominal pain. One person with hay fever who had obtained good relief with the medication subsequently developed bronchial asthma.

Schiller and Lowell³⁹¹ found Trimeton effective in forty-seven of fifty-five patients with perennial allergic rhinitis, reporting satisfactory or partial relief; thirteen of fifteen with hay fever and twelve of twelve with urticaria. The relief of symptoms usually occurred within thirty minutes and lasted for more than three hours. The drug failed to relieve one patient with vernal catarrh and one with atopic dermatitis. Drowsiness was seen in six of the patients with dryness of the mouth in three and weakness in one. Goldman³⁹² treated eighty patients with various allergic syndromes with doses of 12.5 mg. three times daily, or 25 mg. every four hours. Sixty-one of the patients had complete temporary symptomatic relief, with two reporting 50 per cent relief, and no improvement being noted in seventeen. In his series, the drug provided no relief when bronchial asthma was present. Side effects include sleepiness in three patients and insomnia in one.

Allison and Robinson³⁹³ treated thirty-six patients with allergic syndromes with Chlor-Trimeton (2 to 4 mg. three times daily). Relief was reported in three of three

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patients with dermographism, one of four adult patients with atopic eczema, two of three children with atopic eczema, six of seven with urticaria, four of five with angioneurotic edema, one of two with bronchial asthma, five of five with seasonal hay fever, two of three with vasomotor rhinitis, one of two with dermatitis venenata, and one case of pruritus vulvae. Only one patient reported an undesirable side effect, namely paresthesia. Vickers and Barrett³⁹⁴ also showed the drug to possess high therapeutic efficiency and low toxicity. Gaillard³⁹⁵ administered Chlor-Trimeton to 332 office patients, presenting over 550 symptoms or syndromes, including hay fever accompanied by bronchial asthma, hay fever, asthma due to pollen or infection, infective allergic and other types of vasomotor rhinitis, urticaria and miscellaneous affections, potentially allergic in origin. Groups of eight, 157, 158 and nine were respectively given doses of 1, 2, 4 and 8 mg. three times daily. On the 2 to 4 mg. dose four times daily, twenty-two of twenty-nine patients with pollen asthma achieved good or fair results, as did fifty-four of sixty-six with mixed (allergic and infectious) asthma, nine of forty-six with intrinsic asthma, twenty-one of thirty with vasomotor rhinitis of various origins, seven of ten with urticaria and angioneurotic edema, one of sixteen with eczema and dermatitis, one of one with vertigo due to pollen and one of four with migraine. Thirty-nine per cent of the patients were aware of the effect of the medicine within 15 minutes, with 44 per cent reporting the effect as occurring in 15-30 minutes. Eighty per cent of the patients reported effects within thirty minutes for all dosages. The high and low doses both lasted equally long, from six to twelve hours. Considering all of the cases of hay fever together, 82.8 per cent of those receiving the 2 mg. dose and 77.4 per cent of those receiving the 4 mg. dose achieved improvement. The author concluded that doses no greater than 4 mg. were satisfactory. The incidence of side reactions was 10.8 per cent, the most frequent being slight drowsiness, one patient complaining of vertigo, two patients on 4 mg. doses having gastrointestinal upsets. The author concludes that the drug has an extremely low toxicity and is likely to cause no more than three per cent of severe side reactions.

In summary, it appears that the antihistaminic drugs are suitable only for symptomatic relief. In general, they do not appear to affect the formation of antibodies or the antibody-antigen reaction. When the drugs are discontinued, the symptoms return if the conditions leading to the allergic state have not changed. The antihistamines are most effective in conditions involving surfaces which have a good vascular supply, including the skin and mucous membranes, and which may reasonably be considered to arise through the mediation of histamine. Thus, urticaria, including that due to drug reactions, and hay fever appear to show the highest incidence of relief in that order. The cough sometimes associated with asthma may be alleviated, although the bronchospasm is not, excepting by intravenous or aerosol medication. Conditions involving deep-seated allergic states, that is, tissues where equilibrium with the humoral system is not as readily attained, are less affected by the antihistaminic drugs. This appears true in those conditions in which "intrinsic" histamine is already within the cells as compared to "extrinsic" histamine which must reach and affect cell surfaces of distant shock organs.

Antihistaminic drugs are also less effective in conditions where histamine may not be the mediator or may be only one of the mediators. Such are not as readily relieved and may not at all be affected. This is not surprising in drugs which have been tailored for their specific activity against histamine. Some drugs have activities other than their antihistaminic action and thus relieve conditions not related to histamine action.

The antihistaminic drugs have found considerable application as pharmacological tools for differentiating between conditions presumably due to histamine and those due to other agents, both in research and in diagnosis. Their reliability in this

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respect necessarily depends on their antihistaminic specificity rather than upon the multiple action effects, true of almost all at present available.

In the following list designations of compounds beginning with "F" refer to Fournneau compounds; those with the letters "RP" to products of the laboratories of the Société des Usines Chimiques Rhône-Poulenc of France. Such compounds have been arranged in the order of the alphabet for ease of tabulation.

In searching the literature, the same compounds may be found under different designations. This is frequently true of the chemical name since some indices or authors may prefer to designate the compounds as derivatives, for example of ethylenediamine, while others may wish to consider them as derivatives of pyridine. Moreover, the usual procedure seems to be to announce the compound first by its chemical name, if its structure is known, or its laboratory number, then when the product appears to have real value, a shortened designation generally a combination of letters and numbers as 3015 RP, followed by a brand name when the compound is ready for commercial use. Literature concerning a given product will contain references in all three types. For this reason, and to simplify ready application of the table, the compounds have been listed under a number of headings, with cross references.

For lack of space, many compounds have not been listed. This includes many of the earlier compounds which were found to be of slight value or were too toxic for human use. An attempt has been made to include the compounds more frequently encountered in the medical literature.

The compounds are listed alphabetically under the identifying number or common or commercial name. Space does not permit listing under the various chemical headings that might be employed.

LIST OF ANTIHISTAMINIC PREPARATIONS AVAILABLE (JANUARY 1, 1950)

- A 446 see Linadryl
- A 524 see Benadryl
- AH 42 see Thenylene
- Amidryl see Benadryl (A/S Medicinalco, Copenhagen (tablets 0.5 gm.)
- Anahist (Anahist Company, affiliate of Nepera Chemical Company)
active ingredient Neohetramine (25 mg.)
- Antamine (Grove Laboratories)
pyranisamine maleate (25 mg.)
- Antastan (Ciba), see Antistine
- Antazoline, see Antistine
- Antergan RP2339 (Rhone Poulenc), Lergitin; Dimetina; B 97; Bridal
N'phenyl-N'benzyl-N-dimethyl-ethylenediamine
N-dimethylaminoethyl-N-benzylaniline
N-B-dimethylaminoethyl-N-phenylbenzylamine
(tablets 0.1 gm.; ampoules 0.05 gm.)
- Anthallan (Medico Chemical Corporation of America)
lactone of B-gallic acid ethanol-2-di(n-butylamine)
3'di(n-butyl)aminoethyl-4,5,6-trihydroxybenzo(1,2c)furan-1'(3') one
- Anthisan (May and Baker); Neoantergan; RP 2786; see under Neo-Antergan
p-methoxy benzyl-pyridyl-dimethyl-ethylene diamine
- Antistin (a,e) (Ciba); Antastan; phenazoline hydrochloride, M 5512
2 (phenylbenzylaminomethyl) imidazoline
(2-methyl-2-imidazoline) benzylphenylamine
2-(N-benzyl-anilincmethyl)2-imidazoline
- Scored tablets 100 mg.; ophthalmic solution 0.5% pH 6.94; Nasal
solution 0.5%, pH 6.2
- B97, see Antergan
- B 194
- N,N,dimethyl,N'-2-thiazoly,N'-p-methoxybenzylethylenediamine hydrochloride

Diphenhydramine, see Benadryl
Doxylamine succinate, see Decapryn
Dramamine (Searle) dimenhydrinate
Compound of B-benzohydryloxy-N, N-dimethylethylamine and 8-chlorotheophylline; B-dimethylaminoethylbenzohydryl ether 8-chlorotheophyllinate
diphenhydramine compound with 8-chlorotheophyllin
(Tablets 100 mg.)
Hetramine (RP 2971)
N,N-dimethyl,N'-benzyl-N'-(alpha pyrimidyl)ethylenediamine
2[benzyl (2-dimethylaminoethylamino)]pyrimidine
Histadyl (Lilly) Thenylpyramine, Thenylene (Abbott); Meth(h)apyrilene, AH 42;
Lilly 01013
N'-pyridyl-N'-thenyl-N-dimethyl-ethylenediamine HCl
(Capsules 25, 50, 100 mg.; coated tablets, 50 mg., syrup, 4 mg./c.c.; parenteral solution, 20 mg./c.c.; cream, 2%; ophthalmic ointment, 0.5%)
Histagon B (Lederle), see Bromothen
Histagon C (Lederle), see chlorothen
Histaphene (Union Chimique Belge, Brussels)
p-methoxy-benzhydryl-dimethylaminoether HCl
N,N-dimethyl-beta(4-methoxy-benzohydryloxy)ethylamine
Histostab (Boots Pure Drug Co., England)
2-phenylbenzylamino methyl imidazole methane sulfonate
Hydryllin (Searle)
(Diphenhydramin 25 mg.; aminophylline 100 mg.)
Benadryl and aminophylline
Hydryllin with racetephrine, 25 mg.
Inhiston (Union Pharmacal Co.)
Trimeton 10 mg.
1-phenyl-1-(2-pyridyl)-3-dimethylaminopropane
Kriptin (Whitehall Pharmacal Co., American Home Products)
Pyranisamine maleate (Neo-Antergan) (25 mg.)
Lergitin (Recip, Stockholm), see Antergan
Linadryl; A 446
beta-morpholino ethylbenzohydrylether
M 5512, see Antistine
Mepyramine maleate, see Neo-Antergan
Met(h)apyrilene, see Thenylene, Histadyl
Neo-Antergan (Merek) RP 2786; Anthisan; Pyranisamine; Antamine; Kriptin
N-p-methoxybenzyl-N'N'-dimethyl-N-alpha pyridylethylenediamine maleate
N-dimethylaminoethyl-N-p-methoxyamino pyridine
2-(Beta-dimethylaminoethyl)p-methoxybenzylamino pyridine maleate
(Tablets 25, 50 mg.)
Neohetramine (Nepera, Wyeth) Anahist; Thonzylamine, NH 188
N,N-dimethyl-N'(p-methoxybenzyl)N'-2-pyrimidyl)-ethylenediamine HCl
(Tablets 25, 50, 100 mg., Syrup 6.15 mg./c.c.; Cream, 2%)
Nethaphyl (Merrell)
Combination of nethamine and betaphyllamine
Nethaprym syrup (Merrell)
Nethamine HCl 25 mg., theophylline 50 mg., Decapryn succinate 6 mg.
NH 188, see Neohetramine
NU 1504, see Thephorin
Orthoxicol (Upjohn)
(1 c.c. contains dihydrocodeinone bitartrate 36.5 mg., orthoxine, HCl 338 mg., hyoscamine HBr, 2.0 mg., sodium citrate, 6.5 gr.)

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Orthoxine

beta (o-methoxyphenyl)-N-methylpropylamine HCl
alpha, N-dimethyl-o-methoxyphenethylamine HCl

Pentryl (Maltine Company)

methapyrilene HCl 50 mg., ephedrine HCl 16 mg., phenobarbital sodium 16 mg., with and without enteric-coating

Perazil (Burroughs Wellcome); Chlorcyclizine; Compound 47-282, Di-Paralene (Abbott, 1HCl)

1-(4-chlorobenzhydryl)4-methyl piperazine 2 HCl
N-methyl, N'-(4-chlorobenzhydryl) piperazine 2 HCl
Capsules 50 mg.

Phenazeline HCl, see Antistine

Phenergan (Merck Laboratories, Poulenc Frères de Canada, Montreal)

RP 3277; promethazine, Vallergine (May & Baker, England)

N-(2-dimethylaminopropyl) phenothiazine

10-(2-dimethylaminopropyl) isopropylphenothiazine
dimethyl amino-2-propyl-1-thiodiphenyl amine
Special coated tablets, 25 mg.

Phenindamine, NU 1504, see Thephorin

Pinex Antihistamine Tablets

Promethazine, see Phenergan

Prophenpyramine, see Trimeton

Prephenpyridamine, see Trimeton

Pyranisamine, see Neo-Antergan

Pyrathiazine, see Pyrrolazoate

Pyribenzamine (Ciba) CS 63, RP 2750 Tripeleannamine HCl, Pbz
betadimethylaminoethyl-2-pyridylbenzylammonium chloride
N,N-dimethyl-N'benzyl-N' (alphapyridyl) ethylenediamine
2[benzyl(2-dimethylaminoethyl)]aminopyridine

Scored tablets 50 mg.; Elixir 7.5 mg./c.c.; ointment and cream, 2%, nasal solution, 0.5%

Pyribenzamine expectorant with ephedrine (Ciba)

Each 4 c.c. contains pyribenzamine citrate 30 mg., ephedrine sulfate 10 mg., ammonium chloride 80 mg.

Pyrrolazole Abergic (Upjohn) Pyrathiazine; 1 WBR 86

(beta pyrrolidinoethyl) phenothiazine
betapyrrolidine ethylphenothiazine HCl
Tablets 25 and 50 mg.

Resistab (Bristol Myers)

Thonzyllamine (Neohetramine) 25 mg.

RP 2339, see Antergan

RP 2740, see Diatrin

RP 2750, see Pyribenzamine

RP 2786, see Neo-Antergan

RP 2971, see Hetramine

RP 2987, see Diparcol

RP 3015 Searle 1627

10 (betadimethylaminoethyl)phenothiazine; dimethylaminoethylthiodiphenylamine

RP 3277, see Phenergan

RP 3356

10-betadiethylaminopropyl phenothiazine

S 51, see Benadryl

S 108 Schering, see Trimeton

S 1923 (Searle)

N-hydroxyethyl(methylaminoethyl)phenothiazine

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Searle 1627, see RP 3015

Searle 1695

8-chlorotheophylline salt of 10 (betadimethylaminoethyl)phenothiazine (RP 3015)

Serial 01013 (Lilly), see Histadyl

Spofa III

1-(betabenzohydroxyethyl piperidine)

Tabein (Miles) Thenyl pyramine hydrochloride 30 mg. acetophenetidin 0.2 gm. caffeine 0.03 gm.

Tagathen, see chlorothen
chlorothen citrate

Theneffren (Abbott)

Thenylene hydrochloride 50 mg., ephedrine hydrochloride 25 mg.

Thenfadil (Sterling-Winthrop) WIN 2848

X, N-dimethyl N'(3-thenyl)N'(2-pyridyl)ethylenediamine

2[(B-dimethylaminoethyl)(3-thenyl) amino]pyridine

Thenyl DPE (Stamford Research Laboratories) Thenylene, Histadyl
N,N-dimethyl-N'(2-pyridyl)-N'(2-thenyl)ethylenediamine hydrochloride

Thenylene (Abbott) AH 42, Serial 0103 (Lilly); Histadyl; W 53 (Warner)

Metapyrilene; Thenyl DPE, Thenylpyramine

N,N-dimethyl-N'(alphapryridyl)-N'-(2-methylthienyl)ethylenediamine

N'-pyridyl-N'thenyl-N-dimethylthienylethylenediamine

2[(2-dimethylaminoethyl)-2-thenylamino]pyridine

(Tablets 25, 50, 100 mg.; cream, 2%)

Thenylpyramine, see thenylene

Thephorin (Hoffmann-LaRoche) NU 1504; phenindamine acid tartrate

2 methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene hydrogen tartrate

Tablets 25 mg., syrup 10 mg./4 c.c.; ointment, 5%; lotion, 5%)

Thephorin AC (Hoffmann-LaRoche)

Thephorin acetylsalicylic, acetophenetidin, caffeine

Thonzylamine hydrochloride, see Neohetramine

Tostramine

B-thymoxyethyl dimethylamine

Trimeton (Schering) Prophenpyridamine; S108, see also Inhiston

1-phenyl-1-(2-pyridyl)-3-dimethylaminopropane

2-[alpha(dimethylaminoethyl)benzyl]pyridine

Scored tablets, 25 mg., Elixir, 7.5 mg./4 c.c., Cream, 3%

Tripel-enn-amine, see Pyribenzamine

Vallergine (May & Baker, England), see Phenergan

W 50, see Diatrin

W 53 (Warner), see Thenylene

1WBR 86, see Pyrrolazote

Win 2848, see Thenfadil

47-83 (Wellcome Research Lab)

1-benzohydroxyl-4-methyl-piperazine

75 Bay State Road (Dr. Brown)

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SKIN REACTIONS

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with each organism? Or is there a common antigen or even irritant in all of them? These questions cannot be answered with finality at present. The fact that children and adults react so regularly to all of these bacteria is quite different from the clear-cut specificity noted with such substances as tuberculin, coccidioidin, and histoplasmin. It is obvious that the delayed reactions noted with the common bacteria cannot be accepted as specific without further evidence.

SUMMARY

1. Tuberculous patients were tested with immunogens and bacterial residues of common bacteria.
2. No specific immediate type reactions were noted with either material.
3. Delayed reactions occurred with both materials on all the children and adults tested.
4. The regularity with which such delayed reactions occur suggests the probability that they are due to a common antigen or irritant.

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News Items

ASSOCIATION OF ALLERGISTS OF SOUTH SWEDEN

On May 6, 1950, the Association of Allergists of South Sweden met at the auditorium of the Radiology Clinic, Hospital Building, Lund, Sweden. After the business meeting the following program was presented: "Rh-isoimmunization" by Dr. B. Broman, Stockholm; "Observations Made During Tests to Develop and Suppress, Intentionally, the Production of Anti-Rh-agglutinations" by Dr. Rune Grubb; and "The Significance of Rh Research for the Science of Allergy" by Dr. Paul Kallós.

PERMANENT COMMITTEE ON PEDIATRIC ALLERGY

At a recent meeting of the Board of Regents at St. Louis, a committee on pediatric allergy was established. Dr. Bret Ratner of New York was invited to become chairman of this committee, with power to appoint the membership of the committee. The new members are Dr. William P. Buffum, Dr. Norman W. Clein, Dr. Susan C. Dees, Dr. Jerome Glaser, Dr. Edward Scott O'Keefe, Dr. Meryl M. Fenton, Dr. Albert V. Stoesser, and Dr. Bret Ratner, Chairman.

COMMITTEE ON PSYCHOSOMATIC ALLERGY

The Board of Regents unanimously decided that a Committee on Psychosomatic Allergy be appointed by President Mitchell and Dr. H. A. Abramson, to work with Dr. Stoesser in setting up a group of papers for one morning session at the next annual meeting. The committee is as follows: Dr. D. Baruch, Dr. Hal M. Davison, Dr. Loraine O. Dutton, Dr. Bennett Kraft, Dr. Hyman Miller, Dr. John H. Mitchell, Dr. Murray M. Peshkin, Dr. Boen Swinney, and Dr. H. A. Abramson, chairman.

BRITISH ASSOCIATION OF ALLERGISTS

The ninth general meeting of the British Association of Allergists was held on July 8, 1950, in the Sir William Dunn School of Pathology, South Parks Road, Oxford, England. After the Council meeting, Sir Howard Florey, F.R.S., Professor of Pathology, University of Oxford, acted as chairman of the morning session. Dr. A. W. Frankland spoke on "The First European Congress of Allergy." Dr. Homer Prince of Houston, Texas, presented his paper, "Histamine Therapy," written in collaboration with Dr. Richard L. Etter; discussion by Dr. Blair Macaulay of Liverpool followed.

The afternoon session was presided over by Dr. R. L. Vollum, director of Public Health Laboratory, Oxford, and bacteriologist to the United Oxford Hospitals. Dr. Boen Swinney of San Antonio, Texas, read "Viral Allergy," followed by a general discussion by members and visitors. Dr. Ethan Allan Brown of Boston, Massachusetts, read "Present Status of ACTH Therapy in the Allergic Diseases," with discussion opened by Dr. Peter Bishop, endocrinologist at Guy's Hospital, London.

Dr. Vera B. Walker is president of the Council; Dr. A. W. Frankland is secretary.

NEWS ITEMS

COURSE IN ALLERGY FOR CLINICIANS

The University of Illinois Allergy Unit, Colleges of Medicine and Pharmacy, Chicago, announces a course in allergy for clinicians to be held from October, 1950, to October, 1951. The curriculum is divided into six sections: Allergy, Medicine, Immunology, Botany and Mycology, Basic Sciences, and Specialties. The course is accredited for one year towards the formal training requirements of either the American Board of Internal Medicine or of the American Board of Syphilology, and is approved for training under the GI Bill of Rights. Enrollment is limited to six students. The fee is \$300 for Illinois residents and \$600 for nonresidents, or by GI contract.

Courses will be given in Sensitization Mechanisms, Respiratory Allergy, Allergy Clinic, Food Allergy, Preparation of Allergens, Internal Medicine, The Acute Infectious Diseases, Electrocardiography, Psychosomatic Medicine, Immunochemistry, Immunology, Botany, Mycology, Pharmacology, Physiology, Pathology, General Dermatology, Otolaryngology, and shorter courses on Endocrinology, Hematology, Ophthalmology, and Statistics.

Further information may be obtained from Ben Z. Rappaport, M.D., Allergy Unit, University of Illinois, College of Medicine, 1853 West Polk Street, Chicago 12, Illinois.

CANADIAN SOCIETY FOR THE STUDY OF ALLERGY

At Victoria General Hospital Auditorium, Halifax, Nova Scotia, the annual meeting of the Canadian Society for the Study of Allergy was held on June 20. The morning session featured the following papers: "Dermatological Allergy" by Dr. K. A. Baird, West St. John, N. B.; "Dandelion as a Cause of Hay Fever" by Dr. H. C. Jamieson, Edmonton, Alta.; "Antibody Studies in Hay Fever in Children" by Drs. S. Pedvis and H. Bacal, Montreal, Que.; "Some Clinical Problems in Allergy" by Dr. I. H. Erb, Toronto.

At the afternoon session the guest speaker was Dr. Kingsley Johnston, Department of Allergy, Cleveland Clinic, Cleveland, Ohio, who presented "Progress in Allergy During the Past Decade." Other papers read were "The Use of ACTH and Cortisone in Diseases of Hypersensitivity" by Dr. Bram Rose, Montreal, Que.; "The Effects of Phenergan in Experimental Allergic Glomerulonephritis in Rabbits" by Dr. J. Fitzgerald, Toronto, and Dr. J. Hamilton, Queen's University; and "Pneumothorax Occurring in Asthma." A special feature was a film, "Allergy, Immunology—Diagnosis and Treatment" directed by Dr. Leo Criepp, Associate Professor of Medicine, University of Pittsburgh.

NEW FEATURE IN THE QUARTERLY REVIEW

The *Quarterly Review of Allergy and Applied Immunology*, published under the auspices of The American College of Allergists, announces a new feature. Arrangements have been made with Dr. Jonathan Forman to add the "Bibliography," formerly appearing in The Letters of The International Correspondence Society of Allergists, to the *Quarterly*. Dr. Forman will be reference editor of this new department. It will include about thirty-five pages in the four issues, averaging twenty-eight references to the page. This valuable bibliography will make the *Quarterly* one of the most complete reference journals in existence today on the subject of allergy.

During the past year the *Quarterly* has published over 2,000 reviews on all phases of allergy and immunology, as well as a comprehensive index to this material. Since the *Quarterly* can be bound by the publisher at a very reasonable price, the references are made readily available and up to date.

NEWS ITEMS

Special articles featuring broad and comprehensive studies of particular phases of allergy will appear in each issue. Negotiations are now under way to secure outstanding special articles for next year.

The subscription rate of the *Quarterly* is \$7.00 a year to subscribers to the *ANNALS OF ALLERGY*, \$8.00 to nonsubscribers (\$1.50 additional postage for foreign countries). Back issues may be obtained at \$2.50 an issue from Bruce Publishing Company, 2642 University Avenue, St. Paul 4, Minnesota.

BRAZILIAN SOCIETY OF ALLERGY

The Brazilian Society of Allergy met May 24 in the Noble Hall of the General Polyclinic of Rio de Janeiro, with Dr. Ivolino de Vasconcellos presiding. The following program was presented:

- "Historical Panorama of Otorhinolaryngology" by Dr. Antonio R. C. Monteiro.
- "The Life and Work of Santorini" by Dr. Erich Gruen.
- "Beginnings of Medical Teaching in Brazil" by Dr. Ordival Gomes.
- "History of the Leukemias and Pseudoleukemias" by Jayme de Mendonca Castro.
- "Vital Brazil-Pioneer in Fight Against Snake Bite" by Dr. Ivolino de Vasconcellos.

ALLERGY COURSES IN HAVANA

The University of Havana, Cuba, is holding its Tenth Session of Courses on Specialties of Medicine, July 10 to August 19. Courses on the allergic diseases are conducted by Dr. José M. Quintero Fossas, Director of the Department of Allergy of the National Council for Tuberculosis, who is a Fellow of The American College of Allergists. These courses serve as refresher courses and for postgraduate instruction.

CONNECTICUT ALLERGY SOCIETY

The annual meeting of the Connecticut Allergy Society was held with the Connecticut State Medical Society on May 3 in Waterbury. New officers are Dr. Barnett P. Freedman of New Haven, President; Dr. Vincent P. Cenci of Hartford, Vice-president; and Dr. Paul Winer of New Haven, Secretary-treasurer.

ARIZONA SOCIETY OF ALLERGY

Another new allergy society is the Arizona Society of Allergy, organized May 2 at a meeting of the Arizona Medical Association. Officers are Dr. William B. Steen, Tucson, President; Dr. Eugene A. Gatterdam, Phoenix, Vice-President.

PERSONAL ITEMS—ACA MEMBERS

M. Coleman Harris, M.D., F.A.C.A., announces an additional office at Suite 400, Professional Building, Los Angeles 17, California. His original office is at 416 North Bedford Drive, Beverly Hills. Dr. Harris' practice is limited to allergy.

* * *

Ellis April, M.D., F.A.C.A., 1530 16th Street NW, Washington, D. C., has recently been appointed Assistant Professor of Clinical Medicine (Lecturer in Allergy) at the Georgetown University School of Medicine.

* * *

It has recently been announced that the Cuban Allergy Society has honored Clarence Bernstein, M.D., F.A.C.A., of Orlando, Florida, with membership in that group.

BOOK REVIEWS

THE NOSE. By Thomas H. Holmes, M.D., Research Fellow in Medicine; Helen Goodell, B.S., Research Fellow in Medicine; Stewart Wolf, M.D., Associate Professor of Medicine; Harold G. Wolff, M.D., Professor of Neurology; all of Cornell University Medical College, New York. With a Foreword by Warfield T. Longcope, M.D., Professor Emeritus of Medicine, The Johns Hopkins Medical School, Baltimore. 154 pages, 37 figures; frontispiece in colors. Price \$4.50. Springfield, Ill.: Charles C Thomas, Publisher, 1950.

This monograph consists of extremely interesting and unusual direct observations of a qualitative and quantitative nature, revealing that everyday experiences may give rise not only to emotional responses but to significant physiological changes. The authors have demonstrated that the nasal mucous membranes may either shrink or become engorged, producing the well-known "stuffy" or "runny" nose in reactive individuals in situations of conflict as well as in response to differing chemical and physiological stimuli. The authors interpret these as appropriate protective reaction patterns, which illuminate the correlation of emotional disturbances and respiratory illness.

There are thirteen chapters, most of which are followed by a summary and a bibliography. The relation of hay fever and asthma to the intensely hyperfunctioning mucous membrane is demonstrated by figures and case reports. These "life charts" are very interesting and indicate the extreme accuracy and care taken when observing these reactions.

This is not a text on psychiatry, as the psychiatrists, although given credit for interesting themselves in disturbances of the nose with problems of personality adjustment, are criticized because their observations are made "usually without adequate inquiry into the nature and physiologic mechanisms of the bodily changes." The authors attempt to study the man and his nose as a unit, integrating these points of view for the better understanding of the human organism.

The book should be of interest to all who are concerned with disorders and diseases of the respiratory passages and their relationship to other structures in the head as well as to the more distant organs. As usual with Thomas publications, the paper stock is excellent, the printing and the figures very clear. All allergists will profit by reading this unusual monograph.

THE MERCK MANUAL OF DIAGNOSIS AND THERAPY. A Source of Ready Reference for the Physician. 8th ed. Price \$4.50; Thumb-indexed \$5.00. Rahway, N. J.: Merck & Co., Inc., 1950.

The appearance of the eighth edition of this all-inclusive manual is most welcome, and being the new "Golden Anniversary Edition" of the Merck Manual, it exceeds all previous editions in scope. Since the beginning of preparation of the new volume in 1946 by the Merck Medical Division, more than 100 clinicians throughout the United States have served as authors or consultants. The editorial board consisted of the editor and four other physician members, aided by seven assistant editors who also were physicians. Continuing revisions to include new developments were made right up to the publication date, May 1, 1950. This first printing of 75,000 copies was exhausted by orders prior to publication; a second printing is now on the press and will be available July 30. This is the best testimony of its use among physicians.

Approximately 1,600 pages in length, the new edition contains 338 chapters in Part I on the diagnosis and treatment of diseases, 82 more chapters than in the preceding edition. New or expanded chapters include those on nutritional deficiencies; radiation reactions and injuries, including those due to atomic bombs; allergies and antihistamines; psychoneuroses; drug addiction; dental emergencies the physician may have to treat; prenatal and postnatal care; and the care of pre-

BOOK REVIEWS

mature infants. More than 1,175 prescriptions are included, conveniently arranged in categories according to therapeutic action.

All diseases are listed alphabetically, making any subject readily accessible. The section on allergy takes in twenty-nine pages and consists of General Considerations, Allergic Rhinitis, Hay Fever, Perennial Rhinitis, Allergic Conjunctivitis, Bronchial Asthma, Gastrointestinal Allergy, Urticaria and Angioneurotic Edema, Serum Sickness, Physical Allergy, and Prescriptions.

Part II contains new chapters on routine immunization measures, clinical and bedside procedures, laboratory tests practicable for the physician's office, suggested items for the physician's bag, an outline of preoperative and postoperative care, a section on diets, and helpful ready reference data and conversion tables.

The medical experience gained in World War II and the phenomenal advances in medical science since then are reflected throughout the new volume. Some of the other highlights are a complete up-to-the-minute presentation of antibiotic therapy, crystalline Vitamin B-12, Cortisone, and ACTH. Directly following the Foreword there is "Suggestions for Readers," a very helpful page pointing out special subjects in which there may be particular interest. Many of the chapters contain helpful tables; those on Cardiac Arrhythmias and Cardiac Blocks are illustrated by ECG tracings; and a useful miscellany will be found at the end of Part II. This includes recommended daily dietary allowances for men, women, and children; the minimum daily basic requirement of nutrients; various diets used in disease states, with sample menus; food values; food equivalents; office laboratory procedures; alternative proprietary preparations listed as a therapeutic index; ready reference guides of calculation of dosages for infants, children, and aged patients; a table of weights, measures, and equivalents; and an index with headings printed in boldface type.

The book is printed on thin India paper stock in very readable type and bound in a beautiful dark blue durable buckram, which makes it one of the most valuable encyclopedic reference manuals on the physician's desk.



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SOME NEWER ASPECTS OF THE BIOLOGY OF INFECTIOUS MONONUCLEOSIS

LOUIS PELNER, M.D., and SAMUEL WALDMAN, M.D.
Brooklyn, New York

THE purpose of this communication is to discuss certain points in the natural history of a disease with protean manifestations, i.e., infectious mononucleosis. We desire to present the following aspects:

1. An allergic background was observed in all of our cases.
2. Many of the patients presented a relative paucity of granulocytes in the blood, and developed a severe sore throat. Penicillin therapy tided these individuals over until the granulocytes increased.
3. Many of the patients presented evidence of liver damage (hepatitis). This type of hepatitis improved very well with choline or methionine, in direct contradistinction to other types of hepatitis, which do not respond.
4. When Aureomycin became available, we instituted treatment with this antibiotic and noted a rather dramatic response, with subsidence of fever and decrease in size of the glands and spleen.

THE ALLERGIC BACKGROUND

We first noted in 1946 that our patients with infectious mononucleosis had an allergic family history or had classical allergy themselves.¹⁴ The disease was interpreted as a virus infection in an individual that reacted in a special way, i.e., with the lymphatic system as the shock organ. This concept had a very special value at that time, because even if we had no way of attacking the virus, we might be able to slightly alter the substrate with antihistaminic drugs and thus help abort the infection. We have now studied fifty patients,² and in all of these we found an allergic background on careful questioning. One of us¹⁴ reported this finding in 1946, and

¹⁴This article is Number III in a series of articles on "Studies of Liver Dysfunction."

*Dr. Max Blonstein is an Associate Fellow of The American College of Allergists.

²Dr. Max Blonstein allowed us to include some of his patients, which were studied along similar lines.

received diverse reactions from competent students of this condition. One authority²⁰ with a large experience stated that aside from the obvious similarity between serum sickness and infectious mononucleosis (swelling of lymph nodes, lymphocytosis, fever, presence of heterophile antibodies) there was no connection between allergy and the disease under discussion. On the other hand, another internist¹⁹ stated with equal emphasis that he had never seen a patient with infectious mononucleosis who did not have a definite history of allergy. He stated that the episodes of infectious mononucleosis often occurred within a few days following an exacerbation of either asthma or hay fever.

There have been suggestions in the literature that abnormal blood findings suggestive of infectious mononucleosis might be found in cases with clinical allergy. This was noted repeatedly by Randolph and his associates.¹⁵⁻¹⁷ However, they maintained that these cases were not infectious mononucleosis, but were really evidence of "allergic toxemia," due to eating food to which the individual was allergic. Many of their patients had glandular enlargement, fatigue, deep generalized aching, atypical lymphocytes in the blood smear, but negative heterophile antibody tests. It is now conceded that a negative heterophile antibody reaction is not necessarily evidence against infectious mononucleosis.

The concept of an allergic substrate has importance both in diagnosis and treatment. An individual with a past history of allergy, and presenting fever, generalized adenopathy, and sore throat, should have infectious mononucleosis included in the differential diagnosis of his illness and should have the requisite tests done. Before the advent of Aureomycin, our treatment consisted of one of the antihistaminic drugs (Pyribenzamine, Benadryl, Trimeton, 25 mg every four hours) and aspirin 0.3 gram every four hours. This very often caused a dramatic subsidence of the condition in several days. We have recently used this treatment also in two patients who could not tolerate Aureomycin because of severe nausea and vomiting.

Ravenna and Snyder¹⁸ recently noted that about 50 per cent of their patients with infectious mononucleosis had edema of the pharynx, soft palate, and uvula. They felt that finding this diffuse edema in the absence of exudate was a valuable sign for the presumptive clinical diagnosis of infectious mononucleosis. They had one case in which the edema extended into the larynx. This edema might suggest an allergic mechanism at work. There is also a report of a death due to laryngeal edema in infectious mononucleosis.²¹ With an allergic concept in mind, anti-allergic medications can be used.

A rash often accompanies infectious mononucleosis. While this type of rash at times simulates that seen in German measles, we noted that many of our cases presented recurrent urticarial lesions at some point in their illness. This type of rash responded very well to antihistaminic drugs.

TABLE I. H. R. CASE 4. HEMATOLOGY TABLE

Date	Cytology	W.B.C.	Poly-morpho-nuclear	Stabs	Juve-niles	Large Lympho-cytes	Small Lympho-cytes	Mono-ophiles	Eosin-philes	Baso-philes
1/25/49	Downey+	5,600	27%	9%	4%	19%	36%	5%	—	—
1/27/49	Downey+	9,200	26%	8%	—	14%	43%	8%	1%	—
1/29/49	Downey+	11,100	25%	4%	—	17%	45%	8%	1%	—
1/31/49	Downey+	10,400	19%	6%	—	26%	40%	6%	2%	1%
2/3/49	Downey+	9,400	32%	3%	—	10%	47%	6%	2%	—
2/7/49	Downey—	8,600	34%	6%	1%	6%	44%	6%	3%	—
2/10/49	Downey—	6,300	37%	1%	—	3%	52%	3%	4%	—

TABLE II. J. G. CASE 7. HEMATOLOGY TABLE.

Date	Cytology	W.B.C.	Poly-morpho-nuclear	Stabs	Juve-niles	Large Lympho-cytes	Small Lympho-cytes	Mono-ophiles	Eosin-philes	Baso-philes
4/12/49	Downey+	11,700	26%	4%	0%	16%	50%	4%	0	0
4/18/49	Downey+	10,400	22%	1%	0%	15%	58%	3%	1%	0
4/23/49	No Downey	8,00	42%	4%	0	40%	9%	5%	0	0

GRANULOCYTOPENIC REACTION

Sore throat is so frequently seen as part of the picture of infectious mononucleosis that it must be considered one of the symptoms. This refers to the initial sore throat which is seen at the onset of the disease. This often improves, but there frequently develops later a severe ulcerative pharyngitis or acute tonsillitis. Joyce,¹¹ like Bernstein,² believes that the ulcerative pharyngitis and acute tonsillitis are complications of the disease, rather than part of the disease itself, and that the lesions are similar to complications occurring in agranulocytosis. In our cases, the development of a severe pharyngitis could almost always be forecast if the polynuclear cells were relatively few in number (Table I & II). It is true, however, that the degree of severity of the ulcerative pharyngitis could not be exactly foretold by the actual percentage of granulocytes in the peripheral blood. Since a granulocytopenia occurs in nearly every case of infectious mononucleosis, it would be attractive to believe that it was responsible for the lowered resistance to secondary infection of the individual. This, as has been stated, is only generally true.

In the foregoing discussion, we have stressed that a relative, rather than an absolute, granulocytopenia was present during the phase of ulcerative pharyngitis. For example, in one of Joyce's cases the white blood count was 21,050 with 39 per cent neutrophiles, making an actual count of 8,209 neutrophiles per cubic millimeter of blood. Certainly the absolute number of polynuclear neutrophiles is even higher than would be present normally, even though the relative proportion is lower. This finding could be correlated with the development of ulcerative pharyngitis only if there was a mutual antagonism between polynuclear neutrophiles and lymphocytes which would make the force of 8,209 neutrophiles less effective as

guardians against secondary infection than they would otherwise be. This very concept has been noted and discussed by Crofill.⁵

Other work along the same line is the observation that an impure substance extracted from the urine of patients with myelocytic leukemia may temporarily retard the progress of lymphatic leukemia. These observers found that the opposite effect was also true: the material obtained from patients with lymphatic leukemia was claimed to retard the progress of myelocytic leukemia. These materials are known as myelokentric and lymphokentric acids, respectively.^{12,13}

On the basis of the work just noted, we might postulate that there is a mutual antagonism between polynuclear neutrophiles and lymphocytes, and that although a case of infectious mononucleosis may have an absolute polynuclear count as high as or even higher than normal, this force is relatively ineffective in the presence of a tremendous increase in the number of lymphocytes.

Penicillin in daily doses of 600,000 units of procaine penicillin-in-oil tides these patients over this relatively granulocytopenic period. We believe, with Joyce, that penicillin is an important part of the treatment of the complicating sore throat in infectious mononucleosis, in spite of statements by recent authors on the subject of penicillin stating that it should not be used in infectious mononucleosis.⁹

Joyce has also called attention to the "saddleback" type of fever, i.e., a recurrent type of fever, associated with the severe ulcerative pharyngitis. This phenomenon was noted in three of our patients.

TREATMENT OF ASSOCIATED HEPATITIS WITH LIPOTROPIC SUBSTANCES

It would be safe to say that clinical or laboratory evidence of hepatic involvement occurs in at least 60 to 75 per cent of the cases of infectious mononucleosis. Some authors report 95 to 100 per cent^{3,4,8} involvement as shown by abnormalities in the liver function tests in cases of infectious mononucleosis without jaundice. In fact, a highly positive cephalin flocculation test with classical symptoms may speak in favor of this disease in spite of a negative heterophile antibody reaction.

We have found that the earliest symptom heralding liver involvement is severe unremitting nausea, sometimes associated with fullness and belching. In the presence of these symptoms, the cephalin flocculation test would invariably be highly positive (3+ to 4+). Giving these patients choline dihydrogen citrate (tablet gr 10, Lilly, or capsule gr 7.5, Flint) or methionine (gr 7.5 tablet or capsule) every four hours produced a dramatic remission of the nausea and other associated hepatic symptoms within twenty-four to thirty-six hours. We have never observed jaundice in any of our personal cases when the lipotropic substances were started at the onset of nausea. One of our borrowed cases developed jaundice, preceded by nausea three days before. Choline was started when fairly

deep jaundice was noted, and it seemed to improve the symptoms, according to the attending physician.

It has been repeatedly reported that the lipotropic substances do not influence the course of infectious hepatitis. It is our feeling that choline and methionine do quite dramatically affect the hepatitis of infectious mononucleosis. It might be that the hepatitis associated with this condition is of a milder type than true infectious hepatitis.

THE TREATMENT OF INFECTIOUS MONONUCLEOSIS WITH AUREOMYCIN

To date, we have used Aureomycin in eighteen cases of infectious mononucleosis as soon as this diagnosis was made. It seemed to have a remarkable influence in diminishing the fever and the size of the liver and spleen. In two cases, in which it was given early before any liver involvement was noted clinically or by test, hepatitis did not develop. This may have been fortuitous. When Aureomycin was started late in the granulocytopenic-sore throat period, it did not appear to be effective. One limiting factor in the use of Aureomycin is the nausea and vomiting that it induces in a fair number of patients. In two patients we had to return to the treatment with antihistaminic agents to obviate these by-effects.

Aureomycin apparently attacks the virus etiological agent in this condition, while the antihistamine attempts to alter the allergic substrate which we feel is present.

In two of our cases of undoubtedly infectious mononucleosis with relatively low heterophile antibody titers (agglutinations up to and including 1/64), the titers promptly fell after Aureomycin was started. It is possible that Aureomycin stops the development of the disease, but this point requires much further observation.

Aureomycin is given in 0.25 gram capsules every four hours, but the dosage may be increased in severe infections.

ILLUSTRATIVE CASES

Case 1.—LM., twenty-three, a married woman, gave a history that during March, 1947, she was jaundiced for two weeks, then developed what was considered to be a virus pneumonia which lasted four weeks. Following this she developed chills with fever and sore throat for which penicillin was given by hypodermic and by mouth. However, for the following two months she still had sore throat and fever. She was seen by one of us on July 1, 1947. She also gave a history of recurrent bronchial asthma since the age of two, which developed every time she had a cold. Examination revealed a red throat, generalized adenopathy and an enlarged spleen. The white blood count was 13,000, polymorphonuclear cells 45 per cent, lymphocytes 46 per cent and eosinophiles 5 per cent. The heterophile antibody test was positive up to and including a dilution of 1/224. Agglutination tests for typhoid, brucellosis and paratyphoid A and B were negative.

Prybenzamine, 50 mg and aspirin 5 grains were given every four hours; and within seventy-two hours there was a clearing of the redness of the throat, a marked diminution in the size of the glands, and a diminution in the size of the spleen. Within a week the patient was sufficiently recovered to take a trip to a distant city.

INFECTIOUS MONONUCLEOSIS—PELNER AND WALDMAN

Case 2.—A.N., a girl, aged fifteen, complained of fever, severe sore throat, and generalized adenopathy of one week's duration. There was no liver or spleen felt in the abdomen. Because blood work could not be done for several days, a large dose of penicillin was given, which had no effect on any of the symptoms. A heterophile antibody test was positive up to and including a dilution of 1/224. The white count was 14,400, with 44 per cent neutrophiles, 14 per cent large lymphocytes, 33 per cent small lymphocytes, and 8 per cent monocytes. Many large lymphocytes appeared to be in transition to monocytes.

The patient has a marked allergic family history. She, herself, is sensitive to grass and ragweed pollens and dust. Since penicillin and aspirin had previously failed to affect her temperature, she was given Pyribenzamine 25 mg every four hours. In addition, an aspirin tablet was given at the same time. This combination had a remarkable influence on the fever and sore throat. The generalized lymphadenopathy remained for five days longer, and the patient was clinically well in about ten days.

Case 3.—C.E., aged twenty-four, with a previous history of thrombocytopenic purpura ten years previously, became ill with a fever of 103 to 104 degrees and severe unremitting nausea. She was treated expectantly with acetylsalicylic acid and other simple remedies for several days. She was seen by one of us three days after the onset of this illness, and after careful examination we found only a high fever and complaints of severe nausea. Methionine, 1 gm every four hours was given because it was felt that perhaps this nausea was a product of liver dysfunction. After several days of this therapy, the nausea was much improved, but the fever still ranged between 103 and 104 degrees. The mother reported that one day this patient started to sneeze incessantly and that she developed recurrent hives with severe itching over a six-hour period. Another interesting point in her history was that she has a perennial vasomotor rhinitis, which is undoubtedly also of an allergic nature. She was seen again, and this time enlarged lymph glands were found in the neck and axilla. The spleen was enlarged. (The previous condition of thrombocytopenic purpura was treated medically and not by a splenectomy).

The patient was put on Pyribenzamine, and after twenty-four hours the temperature dropped to 100.6 degrees and she felt much better. The glands and spleen had slightly receded. At that visit the liver was also found to be enlarged, so that methionine was continued.

The blood report taken on the first visit showed a positive heterophile agglutination, being positive in dilutions up to and including 1:3584. The white blood count was 12,200, with 12 per cent adult polymorphonuclear, 3 per cent stab cells, 24 per cent large lymphocytes, 54 per cent small lymphocytes, 4 per cent monocytes and 3 per cent eosinophiles. Many of the large lymphocytes showed dark blue vacuolated cytoplasm. Two days later she developed a very severe sore throat without a membrane. A blood count taken on that day showed a total white blood count of 10,500, with 6 per cent adult polymorphonuclear, and 2 per cent stabs. The large lymphocytes showed the characteristics described above. The heterophile agglutination test was still positive in the same dilutions. Penicillin-in-oil was started, 600,000 units daily.

Five days later the white blood count was 8,200, with an adult polymorphonuclear count of 11 per cent and 3 per cent stabs. There were 10 per cent large lymphocytes and 71 per cent small lymphocytes. The large lymphocytes still showed the dark blue vacuolated cytoplasm. Penicillin-in-oil was continued.

From this point on her recovery was uninterrupted. The spleen and liver were normal size and the glands had either entirely receded or had become very small.

Case 4.—H.R., aged twenty-one, was seen on January 25, 1949, with a history of fever up to 103 degrees, severe headache, and pain in the back of the neck. Up to this time he had been on penicillin and aspirin without satisfactory relief and without improvement. He had a slightly infected throat, as well as generalized adenopathy. He had at that time no enlargement of the liver or spleen, and no rash. Agglutinations for typhoid O, typhoid H, paratyphoid A, paratyphoid B, *Proteus* OX19, and *Brucella abortus* were negative. The urine examination was normal. There were no malarial parasites seen on the smear. The heterophile agglutination was considered negative, since there was agglutination present up to and including a dilution of 1:56. The hemoglobin and red blood count were normal. The white blood count was 5,600, with 40 per cent neutrophiles (27 per cent adult polymorphonuclear, 9 per cent stabs and 4 per cent juveniles), 19 per cent large lymphocytes and 36 per cent small lymphocytes and 5 per cent monocytes. Occasional large lymphocytes showed much dark blue cytoplasm with vacuoles. These are the Downey cells seen often in infectious mononucleosis, as well as other virus infections. Cephalin flocculation test done that day, reported two days later, showed a 3+ flocculation in forty-eight hours.

This patient's mother is a highly allergic individual and the patient himself, although not complaining of allergy in youth, stated that he had recently become markedly intolerant of orange juice, developing hives after partaking of even small quantities.

On the basis enunciated previously the patient was given Pyribenzamine, 25 mg every four hours, and an aspirin tablet with each dose. The fever fell to normal in twelve hours and remained at this level throughout the entire course of the illness. He could not take Pyribenzamine for very long because of severe side reactions, so it was changed to Trimeton $\frac{1}{2}$ tablet every four hours. In addition, on this day he complained of fullness, nausea and vomiting; and he was given choline dihydrogen citrate, two 10-grain tablets, three times a day. This caused a prompt remission of his symptoms within twenty-four hours.

The following day the white blood count was 9,200, 34 per cent total neutrophiles, (26 per cent were adult types and 8 per cent were stabs). An occasional large lymphocyte showed the cytoplasm described above. On this day he developed severe pain in his throat, with a heavy grayish-black membrane appearing over a considerable area in the right pharyngeal wall. The throat smear showed occasional Gram-negative coffee-bean-shaped diplococci, occasional Gram-negative rods, and rare *Borrelia vincenti*; but no organisms were seen that morphologically resembled *Corynebacter diphtheriae*. A heterophile antibody test was still negative. Two days later the total white blood count was 11,100, with 29 per cent neutrophiles, of which 25 per cent were adult forms and 4 per cent were stabs. The heterophile antibody test was still negative.

On January 31, the heterophile antibody test became positive, with agglutinations present in dilutions up to and including 1:224. The white blood count on this date was 10,400, with 10 per cent adult polymorphonuclears and 6 per cent stabs, 26 per cent large lymphocytes and 40 per cent small lymphocytes; and the large preponderance of young lymphocytes showed the dark blue cytoplasm characteristic of Downey cells.

Large amounts of penicillin (600,000 units procaine penicillin-in-oil) were given three times daily. There was no marked improvement in the throat pain during the next several days. On February 3, the white blood count was 9,400, with 32 per cent adult polymorphonuclears and 3 per cent stabs. A direct smear of the throat showed the same organisms described above, and a throat culture showed many Gram-negative coffee-bean-shaped diplococci and occasional Gram-negative rods. The

heterophile agglutination test was now negative again. At this time Aureomycin $\frac{1}{2}$ gm every four hours ($1\frac{1}{2}$ gm daily) was given in addition to the penicillin. There was still no apparent improvement either in the pain in the throat or in the membrane. On February 7, the white blood count was 8,600, with 34 per cent adult polymorphonuclears and 6 per cent stabs and 1 per cent juveniles, and the cytology was normal.

These measures were continued until February 10, when the throat was improved. The white blood count at this time was 6,300 and had 37 per cent adult polymorphonuclears and 1 per cent stabs, 3 per cent large lymphocytes and 52 per cent small lymphocytes, with normal cytology. The patient improved markedly. At this time, both penicillin and Aureomycin were discontinued. He was placed on pyridoxine 10 mg three times a day, and folic acid 5 mg three times a day, as well as multivitamin capsules.

Case 5.—S. R., a woman aged 21, first developed a well-authenticated case of infectious mononucleosis while at school during November of 1948. At that time she had generalized adenopathy, headaches and fever. She had what was diagnosed as Vincent's tonsillitis two weeks before this episode. On examination two weeks later, when she had come back home, her glands had receded, but her spleen was still slightly enlarged. Pyribenzamine $\frac{1}{2}$ tablet three times daily was given, as well as vitamin B complex capsules. She improved markedly and was able to return to school within ten days. The patient has hay fever of the ragweed type and is exquisitely sensitive to poison ivy.

The patient was again seen on February 21, 1949, with generalized adenopathy, high fever (104 degrees), and sore throat. She was hospitalized at school, but since she did not improve, she was brought home. When seen on this visit her white count was 4,300, with 33 per cent adult polymorphonuclears, 2 per cent stabs, 15 per cent large lymphocytes, 40 per cent small lymphocytes, 3 per cent monocytes, 5 per cent eosinophils and 2 per cent basophiles, with a moderate number of young lymphocytes showing much dark blue slightly vacuolated cytoplasm. The heterophile agglutination test at this visit was negative. However, she presented undoubted evidence of infectious mononucleosis. She was put on Aureomycin 250 mg every four hours. Within sixteen hours her throat had cleared, the glands had diminished in size and she felt very much improved. Within thirty-six hours the glands had all but become normal in size.

That day, however, the patient developed severe nausea, fullness, vomiting. Suspecting liver dysfunction, although the liver was not enlarged, she was given one tablet (10 grains) of choline dihydrogen citrate four times daily. At that time also a cephalin flocculation test was done which showed a four plus flocculation in twenty-four hours. On choline therapy the nausea, fullness and vomiting ceased and has not returned.

Case 6.—Dr. R. W., aged twenty-two, developed a sore throat, fever and glands in the neck. The fever and sore throat cleared after three days. One week later the patient again developed a severe sore throat, fever of 104 degrees, cough and generalized adenopathy. The liver and spleen were not felt. A blood count revealed 9,300 WBC with 43 per cent polymorphonuclear cells, with 20 per cent large lymphocytes and 33 per cent small lymphocytes. Occasionally large lymphocytes showed the dark vacuolated cytoplasm as seen in infectious mononucleosis. The heterophile agglutination test was positive in all dilutions up to and including 1/223. The cephalin flocculation test was negative. Aureomycin 0.25 gm was given every four hours with a reduction in fever to normal within twenty-four hours, and a remarkable reduction in the size of the glands within seventy-two hours. At this time he

complained of right lower quadrant pain, but as this was accompanied by only slight tenderness and no spasm, a diagnosis of possible abdominal lymphadenopathy was made. In any event, continuation of Aureomycin for two additional days cleared this condition completely. There were no findings in the chest. One day later, he developed itching of the soles of the feet, which was relieved in twenty-four hours with Trimeton, one tablet three times a day. From this point on recovery was uninterrupted and rapid.

Although this patient did not acknowledge any manifestations of allergy himself, it is to be noted that his brother has ragweed hay fever.

Case 7.—J. G., twenty-one-year-old man, college student, complained of a severe sore throat and moderate amount of fever while at college in another state. Two days previously he was stung by a bee, but this did not disturb him. The ensuing two days he developed severe unilateral headaches, associated with nausea and vomiting. At no time previously did he have these headaches. The sore throat cleared promptly with ordinary measures. One week later he developed a sore throat again, but this time with high fever and he was sent home. Examination revealed a reddened throat, generalized adenopathy, a markedly enlarged and tender liver and spleen and a fever of 102 degrees. The patient also complained of nausea. Infectious mononucleosis was immediately suspected, and this was substantiated by the finding of typical Downey cells in the smear, a positive heterophile agglutination test up to and including a dilution of 1/448 and a 4+ cephalin flocculation test after twenty-four hours. Aureomycin was started at once in the dosage of 0.25 gm every four hours; in addition choline dihydrogen citrate 0.5 gm was given every four hours as well. The fever and nausea responded dramatically to treatment. Within forty-eight hours the glands were much diminished. At this time, however, the patient developed a remarkably severe throat, which necessitated daily injections of 600,000 units of penicillin for ten days. Within four days of starting the choline therapy, the liver was normal size, and never again throughout the period of illness was there a complaint of nausea or fullness. The blood counts are noted in the accompanying table.

Although the patient first discounted any history of allergy, a careful inquiry revealed the following: A sister was highly allergic to many foods, the patient himself could not eat chocolate, fish, or spinach without developing hives. During his first year of life he was a feeding problem because of his many food allergies and eczema. Another interesting sidelight in this patient's history was that his sister had recovered from a very severe case of infectious mononucleosis just three weeks previously. Her symptoms were quite different in that she had severe abdominal pain and high fever, and typhoid was suspected for a period of ten days. Following a stormy course, she recovered completely. She has a long history of allergy.

COMMENT

We considered a patient to have infectious mononucleosis if, in addition to the classical signs and symptoms, i.e., fever, generalized adenopathy, sore throat, enlarged liver and/or spleen, there was also a positive heterophile agglutination test, and the presence of Downey cells in the blood smear.

There were four cases with typical signs and symptoms, the presence of Downey cells in the smear, negative heterophile antibody tests, but positive

cephalin flocculation tests. These were considered to be cases of infectious mononucleosis.

For this study, a heterophile antibody test was considered to be positive if there was agglutination in dilution of 1/128 or higher. We know that some authors consider a positive test to be 1/32 or higher, but we found too many non-specific reactions in the latter dilutions.

The term Downey cell, as used in this report, corresponds to the types of atypical lymphocytes described by Downey.^{7,15} The usual cell has a very large nucleus with pronounced chromatin strands. The nucleus has many pale spots, the so-called Osgood's "nuclear fenestrations." The cytoplasm varies in amount; it may be a fine basophilic rim, or if more cytoplasm is present it may have a foamy appearance. Less often other cells are seen with irregular or lobulated nuclei.

We have had no experience with a chronic phase of infectious mononucleosis as described by Isaacs.¹⁰ The symptoms consisted of fatigue, exhaustion, aching of the legs, weakness, depression, afternoon elevation of temperature (99.8 to 101 degrees), moderate splenomegaly, low blood pressure, low blood sugar and the presence of Downey cells in the blood smear. The heterophile agglutination titers in this series were 1/64 or lower, and the symptoms persisted for three months to four years. All of the cases in our report cleared promptly after institution of our methods of treatment. However, Isaacs' patients may have had a true chronic form of infectious mononucleosis which so far has eluded us.

An interesting observation that supports part of our thesis was made by Barnard¹ in discussing Isaac's article. He stated, "Benign systemic lymphosis (infectious mononucleosis), whether acute or chronic, appears to be a reactive state seen in individuals of allergic or atopic constitutions whose lymphoid tissue is the sensitized or shock organ. Such a lymphatic reaction is seen in some persons following the imposition of any stimulus classified among the cholinergic incitants, that is infective, traumatic, radiative, allergic, or even psychogenic affection."

Barnard has extended our observations to other stimuli besides virus infections. The possibilities of this approach appear extremely interesting.

SUMMARY

We have presented some aspects of the biology of infectious mononucleosis:

1. An allergic background was noted in all our patients.
2. Many of the patients had a paucity of granulocytes in the peripheral blood at one phase of the disease.
3. The hepatitis that occurs as part of infectious mononucleosis responds well to lipotropic substances.
4. Automycin in usual doses effectively aborted the disease in eighteen of our patients.

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1352 Carroll Street (Dr. Pelner)
1661 Prospect Place (Dr. Waldman).

PANEL DISCUSSION ON ARTHRITIS AND RHEUMATISM

One of the outstanding features of the Sixth Annual Session of the College will be the panel discussions on arthritis and rheumatism, which will occupy the entire afternoon of February 14, commencing at 2:00 p.m., with Dr. George R. Dickey as chairman. Speakers will be Drs. Wm. K. Hunter, M. G. Bland, M. L. Veller, T. F. Duthie, C. H. R. E. Johnson, A. C. E. T. McLean, and W. C. Service. The complete program will be given in the *Journal of the American Geriatrics Society*.

THERAPY OF RAGWEED HAY FEVER WITH ELECTROPHORETICALLY ISOLATED FRACTIONS (ARTEFOLIN AND TRIFIDIN)

Preliminary Report

H. A. ABRAMSON, M.D., F.A.C.A., M. LOEBL, M.A., H. H. GETTNER, M.A.,
and

B. SKLAROFSKY, B.A.

New York, New York

IT has previously been shown by electrophoretic fractionation that there are numerous components in ragweed pollen extracts which are closely related antigenically.¹ In addition it was pointed out that these components vary widely in their electric charges and that the differences in electric mobility between the components could be used to purify certain of the fractions. By means of the Tiselius technique small quantities of the major colorless component, Trifidin, in giant ragweed pollen extract and the major colorless component, Artefolin, in dwarf ragweed extract had been obtained.

The present communication is a preliminary report of the results of therapy with ragweed antigens rendered essentially colorless electrophoretically. The essentially colorless fractions (approximately 90 per cent of the pigment was removed) isolated by a new method to be discussed in this communication was clinically studied in the summer of 1949 with the kind co-operation of Dr. A. Colmes, Boston, Mass.; Dr. J. Glaser, Rochester, N. Y.; Drs. H. A. Levy and L. Unger, Chicago, Ill.; Dr. L. J. Lieder, Cleveland, Ohio; Dr. A. L. Maietta, Boston, Mass.; Dr. J. H. Mitchell, Columbus, Ohio; and Dr. O. R. Withers, Kansas City, Mo. In this way an independent evaluation of the results of therapy with the mixed colorless pollen extract fractions was obtained.

It was found that with small doses of the colorless fractions in the limited series of fifty-six cases to be presented the results of therapy were about as good as the results obtained with higher doses of the crude mixtures extracted directly from the ragweed pollens as ordinarily administered.

METHOD OF FRACTIONATION

The Tiselius technique was found to be unsuitable for the electrophoretic isolation of large quantities of the colorless material. For this reason a simplified electrophoretic preparative technique was developed which was adaptable to experimental procedures at room temperature.²

Many attempts have been made to adapt the separation of electrically charged ions like proteins to simple equipment operable at room temperature. Membranes, sand barriers, gels, and jellies have been used to immobilize the material and thus prevent convection from mixing the protein

¹ See "The Pollen Allergy Service and the Laboratories of The Mount Sinai Hospital, New York City, and the Department of Laboratories, City Service Harbor, Long Island, N. Y." This research was partially supported by the United States Public Health Service, the National Foundation for Research and Education, and the Research in Pulmonary Disease, New York City.

(or antigen) in a solution, P, with the adjacent buffer solution, B. Tiselius³ points out that aside from optical observations his method increases the potential gradient in the U-tube without undesirable heat convection, simplifies sampling, and avoids disturbing electrolytic processes.

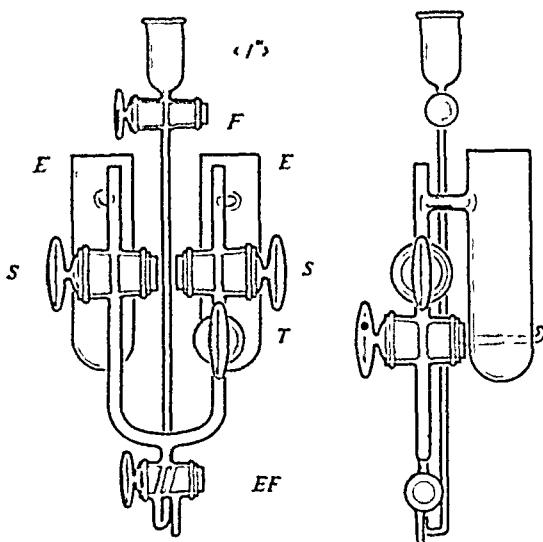


Fig. 1. Front and side views of one design of preparative electrophoresis cell employed. This diagram embodies several different designs found useful. The filling stopcock, F, is used to form the boundary through the two-way stopcock, EF. When EF is rotated and stopcock, S, is open, either the right or left side may be drained and purified material obtained. An alternate method of obtaining samples is to use the tail-hole stopcock, T. Thus, with ragweed extract, the volume of purified Trisidin or Artefolin obtained in twenty-four hours is about 1 cc. Since these solutions may be lyophilized prior to electrophoresis, a comparatively large quantity of antigen may be isolated with this simple procedure.

The equipment for the preparative method described here costs, aside from the source of current, less than \$50. It suitably embodies the advantages of the Tiselius method just mentioned, especially for use at room temperature without any temperature control.

The technique employs a modification of the classical U-tube (Fig. 1) with large side vessels to hold carbons or reversible electrodes. The tail-hole stopcock, T, is used for withdrawing samples at the side. Alternatively a two-way stopcock, EF, at the bottom of the U-tube, is employed both for forming the boundary and for draining the electrophoretically purified fractions from either side of the U-tube. The method depends upon controlling solutions B and P so that they will have different densities, viscosities, pH's, and conductances as follows: Solution B (supernatant) will have a high coefficient of viscosity at the pH of the isoelectric point of the protein contained in solution P, to be immobilized in the lower part of the U-tube. Solution B will have a density considerably less than solution P, so that as the boundary P-B is formed, a well-defined boundary,

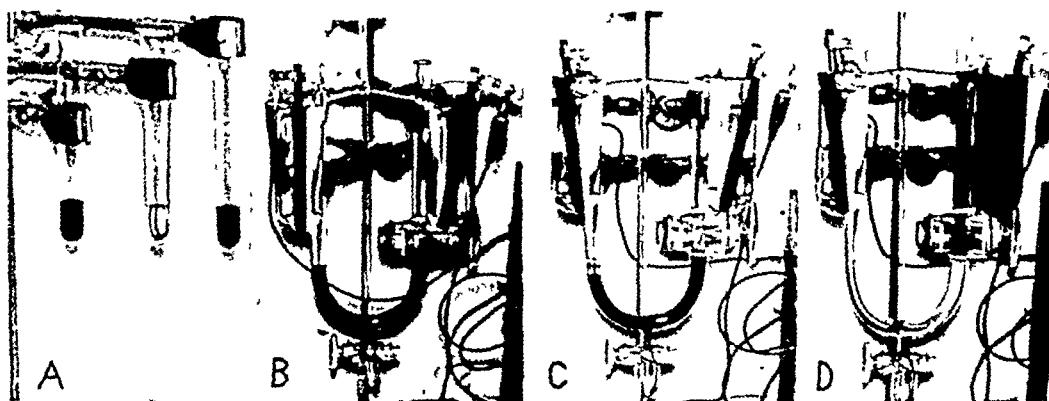


Fig. 2. Four photographs depicting the electrophoretic separation of a charged blue dye from a hemoglobin solution. This is equivalent to separation of the pigments from the major colorless component in pollen extract solutions.

(A) The types of solutions used. In the left test tube is Evans Blue; in the center test tube is the hemoglobin solution; in the right test tube is a mixture of Evans Blue and hemoglobin solutions.

(B) The start of the experiment. The boundary is formed by the hemoglobin-Evans Blue mixture. The lower part of the U-tube contains this mixture (black) in 50 per cent glycerol. The supernatant liquid (light) is 40 per cent glycerol, buffered at the isoelectric point of the hemoglobin. Note the sharp boundaries formed at room temperature.

(C) The experiment after five hours. Note that the boundary has persisted with migration of the Evans Blue (sharp boundary) toward the anode. Some of the Evans Blue can be seen in the stopcock, but both electrode vessels are clear.

(D) The experiment twenty-four hours after starting shows the migration of the Evans Blue into the positive electrode vessel. The colored photographs upon which this black and white photograph is based show that the hemoglobin remained fixed in the lower part of the U-tube with the dye migrating, as illustrated, out of the hemoglobin. These experiments represent how the colorless components of ragweed remain behind with the negatively charged pigments migrating out of the original pigmented ragweed extract solutions, leaving behind the essentially colorless fraction.

stable enough for preparative electrophoresis, results. Typical solutions used by the writer and his co-workers for the past year for the separation of Trifidin and Artefolin, the unpigmented fractions of giant and dwarf ragweed extracts, have been B-40 per cent glycerol at pH 6.8 and P-50 per cent glycerol extract of ragweed pollen. The electrical conductance of solutions B and P in the separation should be regulated so that as little electrolyte as convenient is in P, with a suitable amount in B, to control the pH and drop in potential at the beginning of the separation. For example, in the case of ragweed extracts, no saline was added to the ragweed to be fractionated in solution P. The 40 per cent glycerol in B contained M/15 phosphate buffer at pH 6.8. Thus, initially, the main drop in potential was across the material to be separated, and fractionation was facilitated. A striking experiment (Fig. 2) demonstrating this technique may be made by having solution B at about pH 6.8 employing M/15 phosphate buffer in 40 per cent glycerol, with solution P, a mixture of hemoglobin and T-1824 (a negatively charged dye), in 50 per cent glycerol. At this pH, the isoelectric point of hemoglobin is electrophoretically fixed at the boundaries, whereas the dye, T-1824, migrates out of the mixture to the anode, leaving the hemoglobin with a fairly sharp boundary at the negative side after twenty-four hours.

It may be emphasized that our method utilizes Newtonian or truly viscous liquids. The convection ordinarily resulting from the application of 450 volts to a U-tube, 60 cm long with an internal diameter of 1.0 cm,

at room temperature, is avoided by the use of only high viscosities, not plasticities; and no membranes, jellies, or similar mechanical devices are required. The temperature in the laboratories at Cold Spring Harbor during the summer of 1948 varied considerably over twenty-four hours

TABLE I. COMPARISON OF FORMATION OF CLASSICAL
TISELIUS BOUNDARIES AND THOSE OF THE
MODIFIED TECHNIQUE

Tiselius Method	Method Reported Herein
Conductance B* = conductance P [†]	Conductance B >> conductance P
Viscosity B = viscosity P	Viscosity B < viscosity P
Density B = or slightly less than P	Density B < density P
pH of B = pH of P	The pH of B at or close to iso-electric point of protein to be separated in solution P
Temperature controlled at or near 4° C	Room temperature fluctuations—no temperature control

*Supernatant solution.
†Lower protein solution.

Note that both P and B have Newtonian flow.

but did not disturb the boundaries for preparative purposes during four-day electrophoretic separations. The apparatus can be readily used in an ice chest. If room temperature does not destroy the material to be studied, it is preferable not only because of simplicity but also because the mobilities are greater at this temperature. Table I summarizes the differences enumerated in preparative procedures with the classical method of Tiselius and the method herein described.

Ragweed extracts were made by suspending 10 gm. of ragweed pollen in 100 cc of a 50 per cent glycerol solution. Essentially colorless solutions for therapy were diluted with saline to avoid the pain of the injection of glycerol. This resulted in solutions containing not more than 1000 phosphotungstic acid precipitable nitrogen units per cc for all practical purposes. For this reason the solutions were later lyophilized before electrophoresis, and more concentrated solutions were obtained by this method. Lyophilization may be simplified if the ragweed extract is first dialyzed through No. 36/32 Visking membranes for three hours. However, high losses of active material occur. The dialysis may be followed by studying the electric conductance of the solution being dialyzed, as a function of time. It is suggested that a technique of this sort be used as an end point of dialysis. It would be desirable to avoid dialysis by using better freeze-drying equipment than that available to us.

In order to conserve the ragweed pollen and to shorten the time of the electrophoresis, a modified method was employed from which small quantities of relatively colorless fractions were obtained in twenty-four hours. Three solutions B', P', and B'' of different concentrations of glycerol were employed. Solution B' was M/15 phosphate buffer in 40 per cent glycerol. Solution P' was the lyophilized ragweed extract reconstituted

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TABLE II. SUMMARY OF RESULTS OF THERAPY WITH ELECTROPHORETICALLY PURIFIED COLORLESS RAGWEED ANTIGENS BY VARIOUS AUTHORS IN THE SUMMER OF 1949.

Since it is difficult to evaluate the fine aspects of the results of therapy, two classes only were tabulated. Where the results of therapy were as good as that with the usual mixed antigen or where there is an improvement over a previous season the result is called good; otherwise the result of therapy is designated as poor. Thus a fair result would be considered poor and not good. In the cases of H.A.A. it is felt that the good results were definitely connected with the free use of various types of adjuvant therapy. Adjuvant therapy includes autogenous dust injections, antihistaminic drugs including ephedrine and epinephrine as well as sedation in certain circumstances. All patients treated are included.

Patient	Age	Sex	Clinical Diagnosis	Ragweed Therapy (Previous Year)	No. of Injections of EPR	Total Phosphotungstic Acid Units	Results of Therapy	Adjuvant Therapy	Remarks
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Patients of H.A.A. Huntington, L. I.:

1 DO	6	F	HF & A	Yes	23	600	Good	Yes	
2 WO	34	M	HF & A	Yes	22	685	Good	Yes	
3 JR	10	M	HF & A	Yes	10	90	Good	No	
4 BN	42	F	HF & A	No	37	3700	Poor	Yes	
5 HM	32	F	HF & A	No	14	220	Good	Yes	
6 HM	25	M	HF	No	16	2100	Good	Yes	
7 SZ	13	M	HF	Yes	16	280	Good	Yes	
8 RW	5	M	HF & A	Yes	15	2700	Good	Yes	
9 HS	29	M	HF & A	Yes	20	800	Good	Yes	
10 ML	34	F	HF & A	Yes	15	1850	Good	No	
11 MJ	22	M	HF & A	No	11	165	Good	Yes	
12 GH	9	M	HF & A	No	11	95	Good	Yes	
13 MF	9	F	HF & A	Yes	9	900	Poor	Yes	
14 AD	7	M	HF & A	No	27	840	Good	Yes	
15 EB	23	F	HF & A	Yes	23	1815	Good	Yes	
16 FC	7	F	HF & A	No	18	420	Good	No	

Coseasonal Intra.

Patients of H.A.A. New York City

17 DC	28	F	HF & A	Yes	20	2200	Good	No	
18 DL	30	M	HF & A	Yes	20	4300	Good	Yes	
19 EC	26	F	HF	No	5	10	Poor	Yes	
20 KW	21	F	HF & A	Yes	5	230	Poor	Yes	
21 RS	15	M	HF	Yes	14	400	Good	No	
22 JK	27	M	HF & A	Yes			Poor	Yes	
23 BF	27	M	HF & A	Yes	23	5700	Good	Yes	
24 LL	30	M	HF	No	12	1400	Good	Yes	
25 PI	50	M	HF & A	Yes	19	6600	Poor	No	
26 PG	22	M	HF & A	No	27	13400	Good	Yes	
27 JD	17	M	HF	Yes	18	2600	Good	Yes	

Good for Asthma

Patients of L. L. Maietta, Boston

28 RV	37	M	HF	No	11	200	Good	No	Intradermal
29 MM	14	F	HF	No	12	214	Good	No	Intradermal
30 KT	8	M	HF	No	13	285	Good	No	Intradermal
31 LP	38	F	HF	No	11	310	Poor	No	Intradermal

Patients of J. H. Mitchell, Columbus, Ohio

RT	63	F	HF & A	Yes	12	To Aug. 16, 1949 29000	Poor		
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Patients of J. Oliver, Rochester, N. Y.

12 J.	17	M	HF & A	Yes	12		Poor		No Asthma
13 E.	17	F	HF & A	Yes	6		Good		
24 S.	6	I	HF	No	37		Poor		

RAGWEED HAY FEVER—ABRAMSON ET AL

TABLE II.—CONTINUED

Patient	Age	Sex	Clinical Diagnosis	Ragweed Therapy (Previous Year)	No. of Injections of EPR	Total Phosphotungstic Acid Units	Results of Therapy	Adjuvant Therapy	Remarks
Patients of Herman A. Levy and Leon Unger, Chicago, Ill.									
35 LL	22	F	HF	No	25	1700	Good	Yes	
36 EG	31	F	HF	No	28	4800	Poor	Yes	
37 DG	5	M	HF	No	35	1580	Good	Yes	
Patients of L. J. Lieder, Cleveland, Ohio									
38 CD	44	F	HF	Yes			Good		
39 SG	61	F	HF	No			Poor		
40 JB	14	F	HF	Yes			Poor		Max. dose 5 U followed by severe local reac.
Patients of A. Colmes, Boston, Mass.									
41 KO	40	F	HF	Yes	9	2050	Good		Better than '48.
42 HC	40	M	HF	No	23	2300	Good		Constitutional.
43 AM	26	F	HF	Yes	14	3600	Poor		Highly sensit.
44 BL	35	F	HF	Yes	10	2801	Good		Very sensit.
45 MF	35	F	HF		12	150	Good		Same as old method
46 EA	30	F	HF	Yes	8	3100	Good		Not conclusive
47 NM	36	F	HF	Yes	20	4600	?		Same as old method
48 BR	32	M	HF	Yes	22	11000	Good		Mild constitut.
49 JF	20	M	HF	Yes	13	3500	Poor		Same as old method
50 MH	45	F	HF	Yes	14	4100	Poor		Same as old method
51 JK	27	M	HF & A	Yes	5	2100	Good		Same as old method
52 MG	35	M	HF	Yes		290	Good		Constitutional
Patients of O. Withers, Kansas City, Mo.									
53 RP	28	M	HF	No	24	360	Good	Yes	Asthma preceding season
54 CK	21	M	HF & A	No	20	600	Good	Yes	Poor W. Kan. other pollen. Coseas.
55 RP	23	M	HF & A	Yes	19	110	Good	Yes	
56 BF	21	M	HF	No	11	60	Poor	Yes	

with 45 per cent glycerol to 20 cc. Four cc of solution P' was run through F-EF. Solution B" was M/15 phosphate buffer in 50 per cent glycerol as the second buffer separated from the supernatant by P'.

Another modification of the U-tube consisted of a second tail-hole stopcock so that both positively and negatively charged products can be drained off.

The U-tube is filled with the solution of the concentration of glycerol, B', through EF so that the liquid level rises above the stopcock S. About half an hour is permitted to elapse for test of leakage. After this period, the electrodes are placed in the vessels, E; and the solution B' is run in until the U-tube and the electrode vessels are filled so that the bridge between the U-tube and vessels is also filled. Precautions are taken not to allow any air bubbles to enter the system. The next dense solution, P', is added, approximately 4 cc or enough to fill the tube between the stopcock S and T. This volume must be calibrated for each U-tube. After the solution P' is allowed to run into the U-tube, solution B" is used to raise the solution P' to the desired level.

The foregoing general method has been employed with urea and sugar, using the hemoglobin-dye mixtures, and has been found to be effective, using these materials to form solutions of high and different densities.

RESULTS OF CLINICAL TRIALS

The colorless fraction (on the basis of phosphotungstic acid precipitable nitrogen) used in this series of clinical trials seemed to be less skin reactive than the mixture. What the meaning of this is will be discussed in more detail shortly. The method of electrophoretic preparation was begun in the summer of 1949 and had not yet reached the point to which it has now advanced. For this reason the largest dose was 1,000 PTA units per cc. Table II is a summary of the results obtained by the collaborating physicians mentioned in the introduction and by the writers. Essentially colorless antigens of both giant and dwarf pollen were employed. In all likelihood about 10 per cent of the pigment remained. For this reason the immunologic results are influenced by the presence of a small amount of pigment. The method of deciding whether the clinical results were good or poor was as follows: If the results of therapy were obviously good, they were classified as good. Or if the results were as good as had been obtained previously with the whole extract, they were classified as good. If they were almost as good as previous results, they were classified as poor. In other words, the patients' condition had to be either equal to or better than previous experience or the comparative classification of poor was given. The patients were treated over a wide geographical area so that approximately equal numbers of patients were treated by the writers and their collaborators. As indicated in the table, small doses of pollen allergens were given throughout the season. The number of injections given varied between five and thirty-seven with no regularity essentially observable in the results as far as the number of injections go. A similar lack of regularity exists in the relationship of whether a good or poor result was obtained relative to the dosage.

Let us first consider the patients of the writer treated both in Huntington, L. I., and in New York City. For practical purposes it will be desirable to group these patients together. The writer treated twenty-seven patients with hay fever or with hay fever and asthma with adjuvant therapy in nearly all the cases. The results may be briefly summarized as follows: Twenty-one of twenty-seven were classified as "good." As mentioned, in practically all of these cases adjuvant therapy was employed. This included autogenous dust injections, antihistaminic drugs, ephedrine, and epinephrine with sedation in certain circumstances. Psychotherapy, which takes place in all relationships between doctor and patient, must also be included but this cannot be evaluated at this time. In the writer's series, then, 77 per cent of the patients are classified as good. In the remaining series, the patients of Drs. Maietta, Glaser, Levy, Unger, Lieder, Colmes, and Withers, there were thirty patients. In the thirty patients that were treated, there were twenty-nine usable for classification. Of these twenty-nine cases eighteen cases can be evaluated as having had a good result. In the series of the collaborators, then, 62 per cent are classified as good, the average for the whole series being about 70 per cent. These results are considered

satisfactory as a pilot test of the electrophoretically purified antigens, considering the small dosage employed throughout.

DISCUSSION

Although skin tests made by the writers showed that the electrophoretic fractions were usually less active than the crude mixture, reports from the collaborators indicated that this was not necessarily so. It is possible that the similarity of antigenicity reported previously by the writer for the colorless fraction and the fast-moving pigment fraction as well as other pigments, as far as these experiments went, might have to be modified by future experiments. It is also possible that there were fluctuations in the temperature in the electrophoretic apparatus which may have led to the deterioration during the separation. Different individuals may eventually be shown to have different types of sensitivity to the various fractions. Fractions now being isolated indicate that powerful antigens are being obtained by the method now reported.

It has been shown by ultracentrifugation that the colorless fraction is identical with the main molecule having the highest molecular weight found in the crude mixtures. The value of this molecular weight is about 5000. Reports claiming the presence of "large" molecules often describe¹ contaminated debris present in very small quantity found in colloids of the type studied, or² artefacts produced by prolonged dialysis which lead to the formation of molecular aggregates and artificial systems not found in nature. It is our opinion that in freshly prepared ragweed extracts not subjected to involved laboratory procedures, which inevitably lead to molecular aggregation, the largest molecule present of antigenic significance in the production of and therapy of ragweed pollen hay fever is not much larger than 5000 in molecular weight, exemplified by the electrophoretically homogeneous fractions, Trifidin and Artefolin. It is our working hypothesis, evidence for which is provided in this communication, that this molecule may, in higher doses than that employed here, provide better protection to the patient with ragweed pollen hay fever and asthma than high doses with crude mixtures.

SUMMARY

1. With the co-operation of a group of allergists in different parts of the United States, electrophoretically purified colorless ragweed antigens (Trifidin and Artefolin) were used in the therapy of fifty-six cases of hay fever and asthma.
2. A new preparative method for obtaining these antigens with simplified electrophoretic equipment is described. The method comprises the control of heat convection by using liquids of high coefficients of viscosity and low conductance, making the technique practical at room temperature.
3. Because of losses encountered in purification only small doses of pollen antigen were available for therapy. It was found, on the basis of

this small series, that good results were obtained in 70 per cent of the patients treated. It is believed that (a) in freshly prepared ragweed extracts (not subjected to elaborate laboratory procedures which lead to molecular aggregation) the largest molecule of antigenic significance in the production of and therapy of ragweed pollen hay fever is of the order 5,000 in molecular weight, and (b) it is this molecule that is responsible for the favorable results reported here in the therapy of ragweed hay fever and asthma.

4. This molecule (M.W. = 5,000 approx.) may, in higher doses than that reported here, provide better protection to the patient than the high doses of crude mixtures of ragweed pollen extracts.

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FIRST INTERNATIONAL CONGRESS ON ALLERGY

The American Express Company is preparing itineraries for the first meeting of the International Association of Allergists at Zurich, September 24-29, 1951. Those interested in regular travel will write Dr. F. W. Vattie, Executive Secretary, at 421 Madison Avenue, New York, for complete information.

ANTHOCYANINURIA AND BEET ALLERGY

GEORGE A. ZINDLER, M.D., F.A.C.P., Battle Creek, Michigan
and GEORGE C. COLOVOS, M.S., Kalamazoo, Michigan

ANTHOCYANINURIA, the presence of vegetable pigment in the urine, has been observed by us following the ingestion of beets in individuals manifesting an allergic reaction. Twenty-eight cases are herein presented, twenty-six of which were associated with beet allergy, while the appearance of the pigment in the urine of two seemed to have been related to allergic reactions to other foods coincident with the ingestion of beets at that same time or shortly afterward. It is felt that the presence of an allergic reaction explains why certain individuals manifest this phenomenon after feedings of beets while in others it cannot be demonstrated. To our knowledge the association of anthocyaninuria with allergy has not been previously pointed out.

The first available report of anthocyaninuria was by Jervis¹ in 1914 when he described red urine in the case of a seven-year-old girl who developed sore throat, headache, pain in the abdomen with nausea, vomiting and resulting ketosis after having eaten beets.

Hess and Myers² in 1919 in a paper discussing carotinemia stated that certain children after the ingestion of beets showed a red pigment in the plasma and urine while in others the feeding of extraordinary amounts of beets or beet juice did not produce these findings. They attributed this to an individual variation in the absorption of the pigment.

The experiments of Horwitt³ in laboratory animals are of interest. He made an extract of anthocyanin chloride from Concord grapes and injected it subcutaneously into rats and observed the pigment in the urine. He then fed this extract to rats and subsequently observed it in the feces but not in the urine. The intestinal flora of rats did not seem to destroy this anthocyanin. In a dog the intravenous injection of the extract resulted in its excretion in the urine and the lymph, whereas the intubation of the material with milk into the duodenum of the same dog did not result in pigmentation of the urine. Rabbits fed this anthocyanin were the only experimental animals tested which excreted the pigment in both the feces and urine.

Ruh and Garvin⁴ in 1924 reported thirty cases of anthocyaninuria in children after beet ingestion. Successful attempts to reproduce the condition occurred in only eight out of fifteen of the above cases. They concluded that the inconsistency in producing red urine in all patients after beet ingestion or of reproducing it in the same patient was not due to an "individual variation in the absorption of the pigment" as suggested by Hess and Myers,² nor to an idiosyncrasy in metabolism but was dependent upon the amount of anthocyanin in the beets themselves and to the amount of beets

¹President of the Michigan State Society of Internal Medicine, December, 1932.
Michigan State Medical Society, December, 1932.

Second Vice President, 1933.

ingested. Blood serum was examined in three of the cases of anthocyanuria four hours after beets were eaten and a dull red pigment was observed.

Poole⁸ cited a case of anthocyanuria in 1927 occurring coincidentally with nephritis in which the red color of the urine was thought to have been due to the presence of blood in the urine. The history included unexplained insomnia, restlessness and epigastric pain immediately after meals. However, urinalysis failed to reveal the presence of red cells in the urine, and spectrographic studies did not reveal bands characteristic of hematoporphyrin. The color of the urine changed to yellow when alkali was added and returned to red upon acidification. The presence of the anthocyanin in the urine of this case was attributed to changes in the permeability of the kidneys associated with the nephritis.

Individual cases of red pigment in the urine of well children after having eaten beets were noted by Matheson⁷ in 1936 and Hallé and Girard⁹ in 1938.

Cathala, Martrou and Gras¹ in 1939 observed a patient with beet pigment in the urine without further symptoms and then deliberately re-fed beets to the child and were able to reproduce the pigmentation of the urine. They noted that the urine was acid and on that basis placed three other children on a ketogenic diet, calcium chloride and phosphoric acid so that the urines were pH 4.6, 4.4, and 4.4, respectively. They were fed 125 grams of beets, and in one case the urine remained unpigmented while in the remaining two the urine took on a "roseate tint." On this basis they concluded that the passage of the pigment into the urine takes place in subjects having an acid urine.

Our attention was first drawn to anthocyanuria in the case of a young man seen in 1941 whose family history was positive for allergic disease and who, at the age of twenty-eight, had a gastric resection for peptic ulcer with recurrent bleeding. For the previous ten years he had had hay fever each May and June and recently complained of hives. For several years he had excessive gas and a feeling of fullness particularly after his breakfasts and evening meals. He was aware that wheat, shell fish, chocolate, and tea tended to produce these symptoms. He also complained of chronic constipation with mucus in the stools. X-ray studies revealed a well functioning gall bladder and gastrojejunostomy. The barium enema showed evidence of a spastic colon. The findings on gastroscopic examination were compatible with a diagnosis of a chronic superficial gastritis. Laboratory studies were normal except that the blood smear revealed an 8 per cent eosinophilia. Stool examinations for parasites and ova were negative. Intradermal skin tests to foods and inhalants revealed major sensitivities to wheat, chocolate, string beans, and the grass pollens.

The patient was hospitalized at the time and placed on a diet including wheat and string beans. On one occasion after an evening meal containing wheat and beets he experienced abdominal cramps, nausea, and vomiting. Shortly after the meal he had a bowel movement which was colored red and

noted that his urine was the color of port wine. This urine specimen was examined and found negative for blood pigment; the color changed to yellow upon alkalinization and back to red when acidified, in a fashion observed with beet juice. It was therefore concluded that this might be beet pigment from the meal eaten prior to the collection of the specimen. After the production of these symptoms, wheat, chocolate, string beans, and tea were removed from the diet for several days, and the patient experienced complete relief from his symptoms. During this period he had been deliberately fed beets twice daily in an effort to reproduce the condition, but the urine remained normal in color. He was then fed string beans along with beets at the same meal, which was promptly followed by abdominal cramps, nausea, vomiting and again he passed a port wine colored urine. Subsequently he was fed wheat and beets at the same meal on two successive days with the reproduction of the gastrointestinal symptoms and the appearance of the pigmented urine. At this time wheat, beans, chocolate, and tea along with shell fish were eliminated from the diet with relief of the digestive symptoms, and the patient left town before any further studies with the beet pigment could be made. It was felt that the patient's allergic reactions to wheat and beans had played some role in allowing the beet pigment to be absorbed from the intestinal tract in sufficient quantity to be excreted in the urine.

Searching for possible etiological factors in this case, it was noted that Cathala et al contended that anthocyaninuria was related to the acidity of the urine. We selected three controls at random who were fed large servings of beets three times a day for two weeks after the urine had been maintained at a pH of 4.5 by ammonium chloride administered by mouth. At no time during this experiment did any of the controls have beet pigment in the urine or have any untoward reaction following the ingestion of beets.

After the first observation of this phenomenon we continued to search for other cases. Peculiarly enough this opportunity presented itself in 1946 under unusual circumstances. One of the controls, who had eaten beets three times a day for two weeks without anthocyaninuria in the above mentioned experiment, five years later sought allergic management for headache, nasal stuffiness, fatigue, abdominal cramps and unexplained diarrhea. He had been placed on an elimination diet with relief of symptoms, and then foods were added in the escalator fashion until the diet list was completed. He was found allergic to several foods, so carbohydrate was urged to make up the caloric requirements, and this was taken largely in the form of beet sugar since the patient lived in Michigan where sugar is largely from this source. He had eaten beet sugar several times daily in moderately large quantities over a period of seven months. Beets as such were ingested only occasionally.

His wife also had been under allergic study during the same period for

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severe and frequent headaches with nasal stuffiness which were relieved by combined inhalant and diet therapy. She, too, ate large quantities of beet sugar over the same period of time.

Seven months after the beginning of the allergic diets high in incidence of beet sugar, both the former control and his wife noted red urine after having eaten liberally of pickled beets. Urinalysis revealed the absence of red cells or albumen and also gave negative tests for blood pigment. The urine changed to yellow when alkali was added and returned to red when acidified. The pH of both specimens was 5.

The observation of anthocyaninuria in a patient subsequent to the development of a proven food and inhalant allergy and in whom six years previously we were unable to produce the condition experimentally by massive and prolonged ingestion of whole beets added weight to the original suspicion that allergy played some part in the production of this phenomenon.

After these original observations the former control and his wife deliberately underwent test feedings with beets alone on eleven different occasions and each time clinical allergic reactions were observed, followed in from three to eight hours by the appearance of port wine colored urine.

Three individual eating tests to whole beets were performed on both individuals after the manner originally described by Rinkel¹⁵ and modified slightly by Randolph and Rawling.¹⁶ The husband, or former control, reacted clinically on all three occasions with nasal stuffiness, vertigo, nuchal headache, regurgitation and chilliness. The wife complained of nasal stuffiness, frontal headache with nuchal pain and nuchal muscle spasm. After the experimental beet ingestion, both individuals subsequently showed anthocyaninuria; all six tests were provocative of a leukopenic response of between 40 to 50 per cent in the serial white cell counts such as described by the above authors.

Before any further investigation was carried out, it was deemed advisable to determine whether the pigment in the urine was the same as that found in beets.

The procedure of Pulcher, Curtis and Vickery¹⁷ was used to isolate a quantity of pure pigment from canned beets. The following modifications were made in their procedure. Canned beets were used rather than fresh beet roots since they were fed in this form on the individual eating tests. The beets were first broken up in a Waring Blender and the juice extracted. The beet juice obtained from six No. 10 cans of whole beets was lyophilized. The remainder of the procedure for isolating crude betanin was the same as that given by the above authors. In this way 43 grams of crude betanin were isolated.

Five grams of crude betanin were further purified and crystallized yielding 80 mg of crystalline material. The purified betanin was dissolved in anhydrous methyl alcohol containing 4 per cent hydrochloric acid and an absorption curve was obtained using a Beckman Quartz Spectrophotometer (Fig. 1).

About one liter each of pigmented and normal urine from the same patient was lyophilized. The total solids were 38 grams for the pigmented specimen and 13 grams for the normal. Then 500 mg. of pigmented urine solids were made up to 10 cc using methyl alcohol-hydrochloric acid solvent,

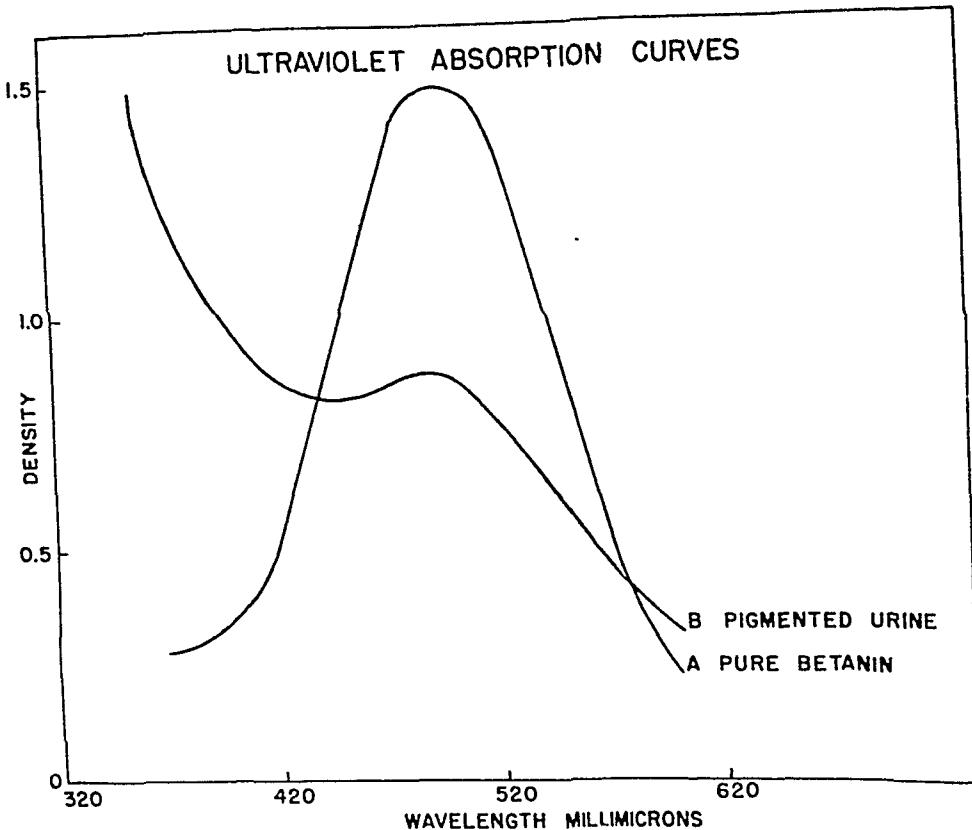


Fig. 1

and 170 mg of normal solids were also made up to 10 cc with the same solvent and used as a blank. Both samples were shaken for ten minutes, and the undissolved solids were permitted to settle out. An ultra-violet absorption curve was run on the clear supernatent.

In Figure 1, Curve A is the absorption curve for the pure beet pigment, betanin; Curve B shows the absorption curve of the pigmented urine. It can be seen that the peaks in curves A and B correspond definitely at about 490 millimicrons. It was therefore concluded spectrographically that the pigment in the urine was the same pigment as that in whole canned beets.

Before any further conclusions were drawn it was felt wise to confirm the fact that controls do not have red pigment in the plasma or urine after massive ingestion of beets. To do this, nine symptomless adult males were selected and instructed to eat a normal supper the night before testing but to avoid alcoholic drinks. They were allowed a glass of water upon rising. They were then fed fifteen small whole

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TABLE I.

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D.	Cases not aware of beet allergy nor anthocyaninuria prior to study, but showed to anthocyaninuria when beets were fed after testing tests to other foods. Subsequently shown to have beet allergy.	J.C. G.I. Allergy; Chronic Fatigue. P.N.A. G.I. Allergy. Chronic Fatigue, Ulnar & Sciatic Neuralgia Headache. P.N.A. Chronic Fatigue Allergic Bladder Severe constant Headaches.	+ + +	Acute Rhinitis Sneezing Coughing	Numbness of Arms and Legs "Dopiness"	Vertigo
A.B.		H.R.			Generalized Nausea-Indigestion	
S.A.		O.M.			Temporal Headache	
		C.H.	+	Giant Urticaria	Abdominal Cramps	
				Itching, Acute Flare of Eczema		
E.	Case of beet sensitivity suspected on basis of clinical reaction to banana ice cream containing beet sugar.	P.S.	None. Used as control and found to be mildly beet sensitive.	Generalized Headache		
F.	Case of beet allergy diagnosed by anthocyaninuria and clinical reaction after eating test to ice cream—while being tested as a control.					

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TITELLETT CONTINUED

canned beets. Urine samples were collected before the feedings and at four, eight, and twelve hours after the beet ingestion. Plasma samples were taken before the feedings and at two, four, and eight hour intervals thereafter.

All the urine samples showed a high specific gravity but no evidence of red pigmentation after the test feedings. All the plasma samples were clear of any red pigment. None of these individuals experienced any symptoms after eating the beets. This, we felt, confirmed the observations of Hess and Myers⁴ that patients not showing anthocyaninuria reveal no sign of that pigment in the plasma after beet ingestion.

To determine whether beet pigment was excreted in the urine on the basis of a nonspecific allergic reaction in itself or whether it appeared as a manifestation of beet allergy, the following study was undertaken. All new patients under allergic management were asked specifically whether they had ever noted anthocyaninuria and all old patients were similarly questioned. If they had, individual eating tests were done with beets. To ascertain whether beet pigment could be absorbed and excreted as an indicator of a nonspecific allergic reaction in a meal composed of beets and a known reactor, beets were fed routinely after each individual eating test to all other foods. This procedure was carried out by instructing each patient at the completion of an eating test other than to beets to eat one-half of a No. 2 can of whole small beets. They were further instructed to restrict fluids and observe the urine for evidence of red pigmentation. If a patient excreted red pigment in the urine after an eating test to another food such as wheat, after which beets were eaten as outlined above, an eating test to beets alone was then done to determine whether the anthocyaninuria was the result of beet allergy alone or whether the beet pigment appeared in the urine as the result of a nonspecific allergic reaction to a food other than beets. These studies resulted in the observation of twenty-five additional cases of anthocyaninuria. It is felt that the circumstances under which these cases were detected are of considerable interest.

Six cases, LD, JG, NP, VB, RW, and RC, were collected who, in their original clinical histories, stated instances of anthocyaninuria following the ingestion of beets but no known or recognized allergic reaction to them, although they were seeking attention for allergic disease. Table I, Group A, shows the clinical reactions to beets after individual eating tests. Each patient excreted red pigment in the urine after the test feedings.

In Group B, Table I, are listed the clinical reactions following test beet feedings of one case, LM, who gave a history of known beet allergy but was not aware of anthocyaninuria after beet ingestion. Red urine was obtained after this test feeding.

Another patient, GM, reacted clinically to three or four common foods tested but did not have red urine after the ingestion of beets at the com-

pletion of the eating tests to these same common foods. He complained, however, of epigastric distress after beets were fed so that an individual eating test to beets was done on that account. It was suspected that the patient had not restricted fluids sufficiently to concentrate the urine so that the pigment could be recognized or he was not sufficiently observant to notice it. When fluids were restricted and the patient instructed to carefully observe the urine after the beet eating test the anthocyaninuria was then detected. The clinical reactions to the experimental feeding of beets alone are listed under Group C, Table I.

Under Group D, Table I, are listed the clinical reactions of five patients after test feeding to beets. These patients were not aware of having anthocyaninuria after beet ingestion nor were they aware of beet sensitivity. These patients, JC, AB, HR, SA, and OM, all excreted red urine after the test feedings to foods after which beets were subsequently fed. Following this, eating tests to beets revealed the listed symptoms. It will be noted that one patient, SA, showed no clinical reaction, but the fact that she improved clinically when beets and beet sugar were eliminated completely from the diet was taken as probable evidence of beet sensitivity.

Under Group E, Table I, are listed the clinical reactions following experimental beet feedings in one case, CH, a child with eczema, who had a clinical allergic reaction of increased itching after the ingestion of banana ice cream. She had been previously tested to milk, to which she failed to react with the production of symptoms. Bananas had been taken in the diet previously without the production of symptoms, so that beet sugar was suspected since it was one of the ingredients of the ice cream. These observations, and the fact that she excreted red urine after beet test feedings and improved clinically when beets and beet sugar were omitted, were taken as evidence of beet allergy. Subsequently she reacted clinically when beet sugar was again reintroduced into the diet. Beet sugar sensitivity will be discussed further later in this paper.

Another case of beet allergy, PS, Group F, Table I, was diagnosed in one of our office nurses who had no known allergies but gave a history of aversion to beets. We were using her for a normal control when she experienced mild clinical symptoms followed by the detection of anthocyaninuria.

Eleven cases, Group G, Table I, including those of the former control and his wife, were studied in which there had been no previous history of anthocyanuria nor of beet sensitivity. Four of these patients, HH, MEB, FB, and HB, had been originally fed beets immediately upon completion of individual eating tests to other foods without having noted anthocyanuria.

Eleven cases, Group H, Table I, including those of the former control and his wife, were studied in which there had been no previous history of anthocyanuria nor of beet sensitivity. Four of these patients, HH,

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MEB, FF, and HB, had been originally fed beets immediately upon completion of individual eating tests to other foods without having noted anthocyaninuria. The other seven had never been fed beets under experimental conditions nor had they previously noted red urine after having eaten beets. The interesting feature in this group is that they had been placed upon elimination diets or rotary diversified diets high in the incidence of beets and beet sugar for various periods of time. Of this group of eleven patients, six, FA, GA, HW, HH, GG, and MEB, had noted clinical reactions in their diet diaries plus the excretion of red urine after having eaten beets. These patients had been on elimination diets containing beets and large quantities of beet sugar. Subsequent eating tests to beets showed clinical reactions as noted in addition to anthocyaninuria.

Five of the eleven patients in this group had been on rotary diversified diets such as described by Rinkel¹⁶ which included the feeding of beets occasionally and the frequent incidence of generous quantities of beet sugar for periods varying from five weeks to two years. Four of these patients, FP, EB, VM, and HB, noted red urine after beets were eaten while on these diets and at the time all were having smoldering allergic symptoms of unknown cause. Individual eating tests to beets were then done, and all showed clinical symptoms listed in Group G, Table I, after the beet feedings. All excreted red urine. Subsequently, when beets and beet sugar were eliminated from the diet their allergic symptoms were relieved. The remaining case, AS, had been on a rotating diet for two years except for the frequent ingestion of beet sugar. She developed chronic allergic symptoms for which no cause could be found; she had never previously reported the excretion of red urine after beet ingestion. An individual food test with beets was done after the avoidance of beets and beet sugar for four days. It resulted in the appearance of the clinical symptoms listed in addition to red urine. Subsequent avoidance of beets and beet sugar resulted in the relief of the chronic allergic symptoms, and the reintroduction of beet sugar into the diet was followed by the reappearance of these same symptoms.

One case, TS, not shown on Table I, is of interest because he is the only case other than the first patient described who excreted red urine coincidentally when beets and a known food reactor were eaten but had neither clinical symptoms nor anthocyaninuria following the ingestion of large quantities of beets alone. Normal compatible leukopenic responses were obtained after eating tests with wheat, corn, and eggs. Beets were fed at the completion of each test without the production of red urine. However, the milk test was followed by the production of a headache and a leukopenic response, and then when beets were fed subsequently the urine contained a red pigment. An individual eating test to beets then failed to produce clinical symptoms or a leukopenic response. The patient did not excrete red pigment when beets were

taken without milk. He refused to co-operate in further studies since he was satisfied that milk was the cause of his headaches.

In an effort to ascertain the incidence of beet sensitivity in this locality among patients studied for major food allergies, seventy-nine patients upon whom individual eating tests were done to foods commonly occurring in the diet were surveyed. These patients had been fed beets after eating tests were completed to other foods. Ten (12.6 per cent) were found to demonstrate anthocyaninuria. These ten patients were studied with individual eating tests to beets and responded with clinical reactions along with the excretion of red urine. Of these ten, five had been previously aware of anthocyaninuria and one of these was aware of beet allergy. Five others had not been previously aware of the excretion of red pigment after eating beets but one of these suspected a beet allergy.

Of these seventy-nine patients, six (7.5 per cent) who had not previously been found to demonstrate anthocyaninuria in the original tests subsequently developed proven beet sensitivity after having been on diets high in the content of beets and beet sugar.

It does not necessarily follow that 12.6 per cent of all allergic patients in this locality demonstrate anthocyaninuria and beet sensitivity, since many allergic patients were seen in whom food sensitivities were of minor importance, or were so obviously sensitive to certain foods that eating tests were not necessary for diagnosis. Furthermore, other patients were seen where the food allergy was of minor severity and the correction of more severe inhalant allergies satisfied the patient. All that can be stated from the figures given are that in food-sensitive patients of a severity necessitating specific diagnosis in the form of individual eating tests, 12.6 per cent were found to be beet sensitive at the onset of the study and another 7.5 per cent developed beet allergy and anthocyaninuria after having been on large quantities of beets and beet sugar in their diets for varied periods of time. While it is appreciated that a difference of opinion may exist as to the need of specific diagnosis for suspected food allergy, nevertheless these figures show that beet sensitivity is a commonly encountered condition. It is admittedly true also that some of these sensitivities were not of a severity necessitating elimination of beet sugar or even beets from the diet.

One wonders whether the allergy to beets may be due to the pigment or beet protein. Efforts to determine this in the two most highly beet-sensitive patients, GA and EA, were inconclusive. Whole beets were treated with concentrated NaOH overnight at a pH of 11. In the morning the pulp was titrated to neutrality with acetic acid. The pigment was thereby destroyed, or at least altered. When the beet pulp so treated was fed to the patients after having avoided beets and beet sugar for four days, they responded with clinical symptoms of nasal stuffiness, headache, and fatigue.

Crude betanin extract 1 from whole beets was fed in 2 gram doses to

these same patients after another four day elimination of beets and beet sugar. These tests were followed by the production of prompt clinical reactions of headaches and nasal stuffiness. No anthocyaninuria was noted though the stools were subsequently colored red. Why the beet pigment did not appear in the urine of these two patients in the presence of clinical reactions we are unable to explain. We feel that no conclusions can be drawn on the basis of this portion of the study without repeating the experiment repeatedly in the same patients and in others. Furthermore, more purified samples of betanin should have been fed. These studies were not done because of the limited quantity of purified betanin available.

We assume that since these same two patients reacted to beet sugar which is highly refined, it is possible these two patients also reacted to the small quantities of beet antigen in the crude betanin. We can assume that the beet pigment, betanin, was not the antigen the patients reacted to because they reacted to the beet pulp in which the betanin was previously destroyed or altered. On the other hand, it is also conceivable that the beet protein also could have been altered at the pH of 11. Our opinion, on the basis of these studies, is that the sensitivity is more likely to beet protein rather than the pigment because the pigment is highly unstable. The combined sensitivity to both the pigment, or its altered fractions, and the beet antigen, or its altered fractions, still remains a remote possibility.

Included in this series of twenty-eight cases presented we have observed five, GA, FA, GG, CH, and AS, in whom we were able to convince ourselves without question of doubt that beet sugar produced a cause and effect relationship between ingestion and the production of allergic symptoms. We obtained individual eating tests to beet sugar in three of these cases, FA, GA, and GG. One complained of frontal headache with nuchal pain, another rhinitis, generalized muscle aching and epigastric pain, and the last nasal stuffiness and severe itching of the nose. The fourth case, CH, who reacted to banana ice cream, has already been described. The fifth case, AS, with smoldering symptoms relieved by the avoidance of beets and beet sugar and reproduced by the reintroduction of beet sugar into the diet, has also been discussed.

Duke² in 1926 described the first case of sensitivity to beet sugar. The possibility of sensitivity to refined sugar at first seemed incredible to us, but the report of corn sugar sensitivity by Randolph and Yeager¹¹ and Randolph, Rollins and Walter¹² lent credence to this possibility. Furthermore, the report of cane sensitivity by Randolph and Rollins¹³ and their subsequent observations of beet sugar sensitivity¹⁴ support our findings.

DISCUSSION

It is difficult to answer the question of why patients who were proven to demonstrate anthocyaninuria after experimental testing were not aware

of the fact that they had previously exhibited this phenomenon. In the first place, individuals eating beets have red stools, and when the patient is a female, no observation is usually made of the urine unless it is collected in a vessel separately. On the other hand, it is of interest that even in the male, red pigment was not previously noted prior to testing. The only answer to this question is that either the patient's attention was not too closely drawn to the color of the urine though it might have been pigmented, or the fluids were not restricted sufficiently after ingestion, or an insufficient amount of beets were ingested to pigment the urine deeply enough so that visible pigmentation could be noted. It should be emphasized here that unless sufficient beets are ingested and unless fluids are restricted following ingestion, the urine may be slightly pigmented an orange color. This can escape detection unless particular attention is paid in observing the color of the urine.

On the basis of the evidence presented, it would seem that in the patient who has developed an allergy to beets, the gastrointestinal tract allows access of the beet pigment into the blood stream from which it is excreted by the kidney. It was originally felt that beet pigment might be used as an indicator in the urine for reactions to other foods. This has not proven to be the case though we are unable to explain why it apparently did so in two of the cases presented. Whether other pigments or dyes may be found to act in this fashion seems worthy of investigation.

Of interest particularly are the eleven patients who were previously not beet sensitive or possibly mildly so, who later developed a definite proven beet allergy on diets high in the incidence of beets and beet sugar and then were able to excrete red pigment in the urine after beet ingestion concurrent with clinical allergic reaction to the beets. If this is the case, it would seem wise to be cautious in the case of allergic patients so that sensitivity may not actually be induced by a diet where this food is urged in generous quantities.

We feel that on the basis of this study it is important to suspect beet allergy where red urine is found after beet ingestion, and in the instances where one is searching for the cause of chronic symptoms, beet allergy should be suspected and beets and beet sugar omitted from the diet for a trial diagnostic period. This is particularly true in areas where the sugar available is largely from beets.

The criterion for the diagnosis of beet sensitivity in this paper has been the production of clinical symptoms after the experimental feeding of beets to patients having previously avoided beets and beet sugar for four days. The test feedings were on the fifth day. We have accepted anthocyaninuria as a valuable aid in the diagnosis of beet allergy. As a rule, leukopenia in the serial white blood cell counts of the individual eating tests to beets showed a high degree of correlation with the clinical reactions. Many of the beet sensitive patients found it was not nec-

essary to eliminate beet sugar from their diets. These patients usually avoided beets as such voluntarily as a result of the clinical tests.

We have studied three patients in whom we felt we were able to produce allergic reactions after test feedings of beets but have as yet been unable to produce anthocyaninuria. These patients, normal in other respects other than their allergic state, all were subjected to a thorough clinical study. No explanation can be made as to why they did not excrete the red pigment even though beets were eaten in large quantities.

CONCLUSIONS

1. Twenty-eight cases of anthocyaninuria are presented. Twenty-six are related to beet allergy, and two seem related to the ingestion of beets along with foods known to have produced allergic reactions.
2. Three patients have been studied in whom clinical reactions are obtained when beets are fed experimentally but no anthocyaninuria detected.
3. Anthocyaninuria seems dependent upon the absorption into the blood stream of the pigment from the intestinal tract during the allergic reaction; it is then excreted by the kidney into the urine. Normal individuals do not absorb detectable quantities of betanin from the intestinal tract.
4. Anthocyaninuria is a valuable sign in the diagnosis of beet allergy.
5. Caution is warranted lest beet sensitivity may be produced in the highly food-sensitive patient by the too frequent and copious feeding of beets and beet sugar.
6. Five cases of beet sugar sensitivity are herein reported.

Grateful acknowledgment is made to Dr. George Pish of the research division of The Upjohn Company for the determination and interpretation of the ultra-violet absorption spectra.

1206 Security Tower

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BRONCHIAL ASTHMA IN SMALL COMMUNITY HOSPITALS

Five-Year Survey

WILLIAM H. LIPMAN, M.D., F.A.C.A.
Kenosha, Wisconsin

THE purpose of this survey is threefold:

First, it presents a statistical analysis of all the bronchial asthma cases coming under hospital treatment in a midwest industrial city of about 50,000 population.

Second, it offers a cross-section of the type of history, diagnosis and treatment by general practitioners in any American community of about the same size and location.

Third, it suggests some improvements in the handling of bronchial asthma.

This review is not intended as a criticism of anyone or any group of physicians or of hospital management *per se*, but rather as a factual study of a group of 157 cases diagnosed as "bronchial asthma" with the thought that the shortcomings revealed may be corrected. The cases were treated by twenty-six general practitioners, all graduates of Class A medical colleges, and with the usual one to two years of internship training plus some years of experience in practice. The two hospitals from which the records were analyzed are 125-bed and 75-bed institutions respectively, and are accredited by the American Hospital Association and the American College of Surgeons. The doctors are all staff members of both hospitals. I have carefully scrutinized and dissected every one of these 157 case histories (of which forty-one are my own) and set down the statistical data in the following break-down charts. This survey, therefore, is a fair index of the type of treatment probably found in any city of like size and location with the possible exception of research medical centers.

Dr. Leon Unger, in his recent book "Bronchial Asthma," defines this disease complex as "an allergic condition characterized by wheezing, dyspnea, orthopnea, and cough, and often associated with rhinitis and with the partial obstruction of the lower air passages."

With this definition of asthma in view, we consider how these postulates have been followed in the present survey of 157 case histories from the Kenosha Hospitals. Of these, sixty-nine were males and eighty-eight females. They were all of the Caucasian race. The ages ranged from eight months to eighty-four years (Table I). The duration varied from three attacks (in two months) in an eight month-old infant to numerous attacks over an interval of thirty-five years in a male of seventy-five. The average duration for the group was 7.1 years. The etiology was

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undetermined in eighty-seven; allergenic in seventy; and sixteen had associated cardiac disease (and so-called cardiac asthma (Table II). Classified according to type (Unger classification), there were forty chronic cases, eighty paroxysmal cases, and thirty-seven cases of undetermined classification (Table III). In only eighteen cases was there any

TABLE I.
TOTAL NUMBER OF PATIENTS

Age	Sex		Total
	M	F	
0 to 10	8	6	14
10 to 20	8	10	18
20 to 30	5	10	15
30 to 40	17	8	25
40 to 50	5	19	24
50 and over	26	35	61
	69	88	157

Family histories: 18.

TABLE III. ETIOLOGY

Undetermined	Allergenic	Associated Heart Disease
87	45 Dust Pollens Epidermals Feathers Foods "Colds"	16
•	45	

**TYPE OF ASTHMA—
UNGER CLASSIFICATION**

Chronic	Questionable	Paroxysmal
40	37	80

Family histories: 18.

family history obtained. The cardinal symptoms of wheezing, dyspnea, cough and orthopnea were listed in a majority of cases, but not in all cases (Table IV). The physical findings were not always listed in the histories, but as nearly as I could determine they are set forth in Table IV. Associated rhinitis was listed in only five cases.

Laboratory studies of this series are listed as is the study of the eosinophile counts of the blood (Table V). The paucity of proper allergic studies (only forty-five of 157 cases) and of eosinophile counts (only forty-three) are also noted; only 10 sputum and nasal smears were done. X-ray examinations were made in only fourteen cases (less than 10 per cent). The x-ray diagnoses made by the roentgenologist are listed in Table VI.

TABLE II. DURATION OF ASTHMA
Average for all—7.1 years

Age	No. Yrs.	Average
0 to 1 year	1	.31 years
1 to 10	14	.662
10 to 20	18	4.8
20 to 30	15	5.1
30 to 40	25	5.35
40 to 50	24	7.7
50 and over	61	11.39

TABLE IV. SYMPTOMS AND PHYSICAL FINDINGS

Symptoms	
Dyspnea	97
Cough	132
Wheezing	131
Orthopnea	27
Fever	13
Associated Rhinitis	5
Abdominal Pain	6
Vomiting	3
Weakness	6
Pain in chest	3
Important Physical Findings	
Râles	113
Cyanosis	15
Emphysema	18
Hyperresonance	9
Prolonged Expiration	9
Tachycardia	2
Ascites	2
Edema of legs	2
Associated Eczema	1
Nasal Polyps	2
Enlarged Cardia	4

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Treatments (Tables VII, VIII and IX) varied from narcotics—morphine, pantopon, codeine, dilaudid, demerol and papaverine in 100 cases to epinephrine in ninety-four cases, aminophyllin in sixty-eight cases, oxygen in sixty-two cases, barbiturates in forty-one cases, iodides in

TABLE V. LABORATORY STATISTICS

Allergic study	45
Blood Smears for Eosinophiles.....	43
Sputum and nasal smears	10

TABLE VI. X-RAY DIAGNOSIS

Peribronchitis	3
Peribronchitis and Bronchiectasis	1
Subacute Bronchitis	1
Peribronchial Fibrosis	2
Chronic Bronchitis	3
Broncho-Pneumonia	2
Lobar Pneumonia	7
Dissecting Aneurysm	1
Total	14

TABLE VII. TREATMENT CHART

Drug	Number Patients Treated	Results			
		Good	Fair	Poor	Death
Morphine	19	5	4	7	3
Pantopon	46	16	16	7	5
Demerol	20	7	8	5	0
Codiene	10	5	3	2	0
Dilaudid	2			1	1
Papaverine HCl	3		2	1	0

TABLE VIII. TREATMENT CHART

Drug	Number Patients Treated	Results			
		Good	Fair	Poor	Death
Epinephrin	94	53	25	6	1
Aminophyllin	68	52	16	6	0
Oxygen	62	36	11	7	4
Antihistamines	23	8	7	5	0
Iodides	15	5	5	4	1
Ephedrine	20	12	3	3	2
Penicillin	30	18	6	5	4
Sulfonamides	6	3	2		1

fifteen cases, digitalis preparations in thirteen cases, penicillin in thirty cases, the antihistaminics in twenty-three cases and isuprel in five cases. The large number of cases treated with the various narcotics is particularly noteworthy, and it is interesting to note that the largest number of deaths (nine) occurred in those patients receiving morphine, pantopon and dilaudid particularly. Also, the poorest results occurred in those cases receiving narcotics, although the lack of serious complications was not noted in a majority of these cases. The large percentage of deaths in the narcotic-treated cases of asthma, as well as the poor response to treatment, coincides with and bears out the views of the leading authorities, who decry the use of narcotics in bronchial asthma.

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The results of treatment (Table X) show that the average hospital stay was 6.16 days and varied from 2.1 days in the infant to 10.65 days in the fifty-year and over age group of patients. It also shows that the most rapid improvement occurred in the younger age groups. In nearly

TABLE IX. TREATMENT CHART

Drug	Number Patients Treated	Results			
		Good	Fair	Poor	Death
Phenobarbital	21	15	3	3	0
Nembutal	10	4	4	1	1
Seconal	9	4	3	1	1
Digitalis	13	3	4	3	3
Calcium					
Gluconate	8	3	2	3	
Isuprel	5	3	2		
Tedral	5	1	4		
Thiamin Chloride	2		1	1	

TABLE X.

Age	Days of Hospital Stay	Degree of Relief			
		Good	Fair	Poor	Death
0 to 1	2.1				1
1 to 10	2.65	11	2		1
10 to 20	5.25	13	4	1	0
20 to 30	6.65	12	2	1	0
30 to 40	8.81	16	6	2	1
40 to 50	8.20	14	6	3	1
50 and over	10.65	15	21	16	9
Averages	6.16	81	41	23	12

every case, several drugs were used and are listed. In many cases, it was difficult to determine which drug gave the primary degree of relief. However, the various drugs and the doses of each were carefully studied in each case and where one particular drug was used most frequently and the response to it was recorded, such drug was considered the primary one in that instance and it was so listed. It will be noted that the greatest relief occurred first with aminophyllin where out of sixty-eight cases fifty-two obtained good relief, sixteen fair and six poor. Next came epinephrine with which fifty-three of ninety-four cases obtained good relief, twenty-five fair, and six poor, and there was one death. Third came oxygen where out of sixty-two cases thirty-six obtained good relief, eleven fair, seven poor and there were four deaths. It must be mentioned that in practically all of these deaths where oxygen was the primary treatment, the patients had previously had other treatments and were *in extremis* on entrance into the hospitals.

The above survey suggests the need of the great improvement in both diagnosis and treatment of bronchial asthma by general practitioners, namely:

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FURTHER STUDIES ON THE USE OF TISSUE CULTURE OF BLOOD LEUKOCYTES IN THE CLINICAL EVALUATION OF BACTERIAL HYPERSENSITIVITY OF THE TUBERCULIN TYPE

HERMANN BLATT, M.D., and FRANK A. NANTZ, M.D.

Cincinnati, Ohio

THIS STUDY concerns a slightly different means of determining sensitivity to specific bacterial strains and, in consequence, a slightly different method of treatment. It follows along lines laid down years ago by Rich and Lewis,¹ Moen,² Aronson,³ Heilman, Feldman and Mann.² In their work on animals, they showed that cells, taken *in vitro* from animals sensitized to tuberculin, became necrotic when subjected to tuberculin, while cells from healthy animals were unaffected. In their experiments, they used both blood leukocytes and the spleen of animals for their tissue cultures.

The present study differs in that only blood leukocytes were used and not those from animals but from man. It also differs in that the matrix used to hold the cells in contact with the bacterial filtrate during the test, was fibrinogen and thrombin instead of plasma. Plasma was naturally tried first, but it was found that the antibodies in the plasma interfered with the action of the filtrate on the leukocytes. After a number of experiments, fibrinogen and thrombin was found to eliminate this difficulty.

In previous studies, cytotoxic indices had been used for measuring the extent to which leukocytes had been inhibited from migrating. By using fibrinogen, however, which has less extraneous material, we could determine necrosis directly.

PROCEDURE FOR OBTAINING LEUKOCYTE SUSPENSION

The citrated venous blood was first centrifuged and the plasma layer so removed that the layer of leukocytes beneath was not disturbed. The leukocytes were then coagulated into a Buffy coat by carefully overlaying them with a layer of calcium Ringer's solution, pipetting off the Ringer's solution, overlaying fresh calcium Ringer's solution and pipetting this off, then overlaying the leukocytes a third time with calcium Ringer's solution and taking it off also. By this time the leukocytes had adhered together sufficiently for the whole layer to hold together while being picked off the layer of red cells.

To dispose of the red cells which clung to the bottom of the Buffy coat, it was laid in a petri dish containing simple Ringer's solution. With a trabisimus hook the red cells were teased away from the Buffy coat. A second or even a third petri dish of Ringer's solution was used to get the Buffy coat reasonably clean.

The Buffy coat was then lifted out and shredded in a Petri dish. The

¹ Presented at the 1937 meeting of the American College of Allergy, New York, April, 1937.
Dr. Rich and Dr. Lewis were Associate Editors of the American College of Allergy.

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shreds were dropped into a bottle containing 3 cc of Ringer's solution, and incubated approximately an hour. During this time such numbers of the leukocytes migrated well up and throughout the Ringer's solution as to form a dense suspension of cells.

DESCRIPTION OF EACH TISSUE CULTURE TEST FOR SENSITIVITY

Ordinary glass slides were prepared with rings or well-walls of vaseline, one for each bacterial filtrate for which a test was to be made. Into each ring, or well, was dropped one drop of full strength thrombin, one drop of cell suspension, and then three drops of the filtrate for which this test was being made. This should have filled the ring to overflowing. The mixture was then sealed in by easing a coverslip atop the vaseline ring, and put to incubate for eighteen hours at 37° C.

Normally, leukocyte cells remain viable for approximately thirty-six hours. Thus, at the end of the eighteen-hour incubation with the filtrate, the cells should, naturally, still be viable. However, many cells of certain individuals had become granular, stippled, crenated or even died out completely in the tests for certain of the filtrates. These individuals, then, were bacterially sensitive, but only to such strains as caused necrosis of their white cells. If no strain caused necrosis, the individual was not sensitive—in other words, normal.

TESTS OF SENSITIVITY TO VARIOUS ANTIGENS

Using this same procedure, leukocytes taken from patients suffering from atopic hypersensitivity were found unaffected by the atopic allergens. This confirmed previous findings.

A reagin containing plasma from patients with atopic sensitivity also, and naturally, had no effect upon leukocytes. Tissue culture studies by other investigators had reported that toxins had no effect. These findings, too, were confirmed.

Histamine in high concentration was also found not to affect the viability of cells.

Diphtheria toxins from two different sources* were used in concentrations as high as 125 to 7000 MLD per c.c., but no necrosis whatsoever was found. Toxins strong enough to kill a guinea pig had no effect upon the leukocytes *in vitro*. In short, necrosis is caused by bacterial filtrates but not pure toxin.

For practical reasons, particular attention was paid to the hemolytic streptococci Group A of Lancefield's classification. Originally, thirty strains were used in the battery of tests for each individual. Now forty-two are used, but this report concerns the tests on only those original thirty.

*The authors gratefully acknowledge the generosity of the Massachusetts Department of Public Health Division of Biologic Laboratories, and the Lederle Laboratories for supplying the diphtheria toxin.

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RESULTS

An analysis of test results was made to discover whether certain strains caused necrosis more often and, if so, which. Two thousand tests were run with Group A hemolytic streptococci strains, of which 213 became necrotic, or were positive. Some strains caused necrosis in as many as twenty-one cases, others in only one or two. There was apparently considerable cross reactivity.

Few patients were positive to only one strain, most to two or three. Frequently, these were relatively unrelated in a serological sense. For this reason, Lancefield's classification on a serological basis ultimately may not be the one to be used. It may be the colony form which is important. An investigation is contemplated to determine which means of differentiating bacteria is most effective.

The blood of 300 patients was tested by a battery of 30 Group A hemolytic streptococci and 70 other bacterial filtrates.

Patients positive to different group A

hemolytic streptococci.....	213
to different <i>Streptococcus viridans</i> strains.....	60
to different <i>Staphylococcus aureus</i> strains.....	56
to different <i>Staphylococcus albus</i> strains.....	42
to different <i>pneumococcus</i> strains types 1 to 14, and.....	21
to various other strains.....	30

To check the accuracy of each test to a given filtrate, a duplicate test was run with blood drawn on a second day. All tests found positive were run a third time. Only those tests which were consistently positive were termed positive, all others were considered negative.

An overall check was made to ascertain the accuracy of the 2,000 tests. Each test was duplicated, and a correlation of 81.8% was found between the two runs. Ten per cent of this "error" can be accounted for by the fact that sterility tests showed an error of 10 per cent. Airborne contamination, especially by molds, is almost impossible to prevent entirely.

DESENSITIZATION OF PATIENTS

Zinner and Grinnell found that bacterial filtrates were most effective in eliciting skin reactions in sensitized animals and that, in skin testing, these filtrates were more reactive than nucleoproteins or whole dead organisms. It would follow, then, that the same broth filtrates should be used in desensitizing the patient as had been used in the tissue culture test which established his sensitivity.

Of the first 158 patients considered positive, 102 were or are being desensitized. To desensitize a patient, a mixture was made of the filtrate to which he had been found sensitive. Dilutions were prepared starting with 1:1,000,000 and increasing in concentration to 1:10,000, 1:10,000, 1:1,000, 1:100, 1:10 and sometimes full strength.

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Before beginning the program of desensitization, a skin test was made on the patient using 1/20 cc of the 1:1,000,000 dilution. Subsequent inoculations, made every three or four days, were increased by 0.1 cc each time—provided there were no reactions. Whenever a reaction occurred, the dosage was repeated until it was well tolerated. Then it was increased again.

Reactions were usually mild and could be classified as local, focal or general. Of the fifty-eight patients then under treatment, eight had general reactions, thirteen focal or general reactions, thirty focal reactions, four local, and two local and focal. The general reactions were febrile; often preceded by a chill. Most reactions occurred early in the course of desensitization, and it was interesting to note that the type of reaction remained constant for each individual patient regardless of the dosage responsible.

Thirty-six patients who were apparently clinically cured, and were down to 1:10 dilution, had their tissue culture tests for sensitivity repeated in duplicate. Of these, thirty-three had then only negative tests; three patients who had been originally positive to several different strains were then negative to all but one strain.

A great variety of initial diagnoses were among those patients tested and treated. Among them were asthma, infectious arthritis, rheumatic fever, rheumatic fever with arthritis, sinusitis, sinusitis with asthma, allergic rhinitis, bacterial-type, recurrent iritis and arthritis, periarteritis nodosa, Christian Schueler disease, and chronic "id" infections.

Characteristic of all patients, a number of those used in this investigation became discouraged before an adequate program of desensitization could be completed. Of 158, fifty-six dropped out. Of the 102 who either completed their program or were still under treatment, not all, six, in fact, had shown no signs of sustained improvement. That, of course, could have been due to either a fallacy in the theory, or to the fact that, though approximately 100 different strains of bacteria were included in the battery of tests, this is but a fraction of the total number to which patients reasonably could be assumed to be sensitive.

It is to be remembered in this regard that patients test positively to more than one strain, rarely to only one. It is therefore possible that, though they were positive to two or three of the strains in the battery, they were positive also to two or three strains for which no tests were made. The very gratifying results obtained, however, with those patients who did complete their series of desensitization inoculations and responded is indicative that further studies along these lines should be made. Of the 102 patients, only six did not improve or only partially improved, but ninety-six lost all their initial symptoms.

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PYROMEN IN THE TREATMENT OF PERENNIAL ALLERGIC SYMPTOMS

THERON G. RANDOLPH, M.D., F.A.C.A., and JOHN P. ROLLINS, M.D.
Chicago, Illinois

INTEREST in the possible therapeutic value of Pyromen arose from the observation that patients developing constitutional symptoms from the administration of intravenous fluids appeared to obtain some therapeutic benefit as a result of those reactions.¹⁰ Since pyrogen contamination is the most common cause of chills and fever following venoclysis and since fever therapy has long been recognized as having therapeutic value, an effort was made to isolate the material responsible for these reactions. This led to the eventual preparation and standardization of Pyromen. As a consequence of this effort the pharmacology of Pyromen has been carefully studied for the past several years.

Extensive laboratory^{2,40-42} and clinical investigations^{8,9,11,12,38} of Pyromen have demonstrated that it is virtually non-toxic and non-anaphylactogenic and may be employed safely within a wide range of dosage. Early clinical studies in neurosyphilis by Lonson and Liebert,⁹ in malignant hypertension by Page and Taylor¹¹ and in dermatologic conditions by Kierland and Kulwin⁸ demonstrated the relative safety of this preparation in the treatment of human illnesses. It should be pointed out, however, that these early clinical investigations were concerned with the use of Pyromen only as a readily controlled pyrogenic agent.

The technique for the detection of bacterial pyrogens as well as that employed for the standardization of Pyromen depends upon the development of a characteristic febrile response following intravenous injection in test animals. This mode of administration in animals is also associated with a blood response consisting of an initial diminution of the total leukocytes and a delayed leukocytosis. The initial leukopenia is characterized by a reduction in number of all white blood cells. The subsequent leukocytosis consists principally of myeloid elements and develops in the presence of a sustained lymphopenia and eosinopenia.²⁰ Identical variations in the cellular elements occur when Pyromen is injected intravenously in man. The similarity of this blood response following an intravenous injection of Pyromen to that following the experimental ingestion of an allergenic food^{12,13} or drug¹⁴ in specifically sensitized allergic patients and to the blood response following the administration of adrenosorticotrophic hormone (ACTH) in animals¹ and human beings,^{2,3,21} and the fact that ACTH is effective in the therapy of allergic diseases^{1,2,3,4} suggested the use of Pyromen in allergy.

Initial observations in allergy patients were made employing Pyromen

¹ Department of Medicine, Northwestern University Medical School.
² Present address: Department of Medicine, Division of Allergy, Mayo Clinic, Rochester, Minnesota.
³ Present address: Department of Medicine, University of Michigan Hospital, Ann Arbor, Michigan.
⁴ Present address: Department of Medicine, University of California, Los Angeles, Los Angeles, California.

in relatively large intravenous doses in an effort to obtain febrile responses between 101 and 104 degrees. Although treatment at a level to accomplish this end impressed us with the therapeutic value of this preparation, the severity of the chills, muscle aching, and fever and the fact that allergic symptoms were sometimes temporarily accentuated following such doses limited its usefulness in the treatment of asthma, dermatitis, and other allergic syndromes. With additional experience it became apparent that a more satisfactory clinical response may be obtained as a result of small doses either not associated with the precipitation of such constitutional symptoms or followed by the development of mild chilling or muscle aching. This preliminary report deals with observations on 150 patients with various allergic syndromes treated with Pyromen since October 1, 1949. The duration of therapy has ranged from ten days to eight months.

THE INTRAVENOUS ADMINISTRATION OF SMALL DOSES OF PYROMEN

The dosage schedule found to be most satisfactory in the treatment of allergic conditions is as follows: 1.0 or 2.0 gamma (micrograms) of Pyromen, diluted in saline to permit accurate measurement, is given as the initial intravenous dose. This may be followed in one to four hours by transient chills or chilliness and is not usually associated with a subsequent febrile response. The simultaneous administration of 0.65 grams of acetylsalicylic acid (providing the patient is not specifically sensitive thereto) often prevents the development of distressing symptoms. In the event that annoying chilling or muscle drawing develops, additional aspirin or the ingestion of approximately a tablespoonful of sugar effectively reduces these symptoms.

A dose of Pyromen that is followed by a chilling response is usually associated with an initial leukopenia followed by a leukocytosis, characterized by a shift to the left of the myeloid elements. There is a coincident lymphopenia and eosinopenia. That this response is not entirely correlated with the production of constitutional symptoms is due to the fact that a similar blood pattern also develops with a slightly smaller dose insufficient to produce such symptoms. A characteristic blood response from the intravenous injection of 5 gamma (micrograms) of Pyromen is shown in Figure 1. It will be noted that in general this is similar to the hematologic response following the administration of ACTH or Cortisone.

The initial intravenous injection of Pyromen is most commonly associated with an improvement in allergic symptoms for a period of twelve to eighteen hours; it may or may not be followed by chilling and other symptoms of reaction. A second dose is usually given forty-eight hours after the first injection, which in turn, is commonly followed by some amelioration of allergic symptoms for a period of forty-eight to seventy-two hours. A third injection is given at the termination of the period

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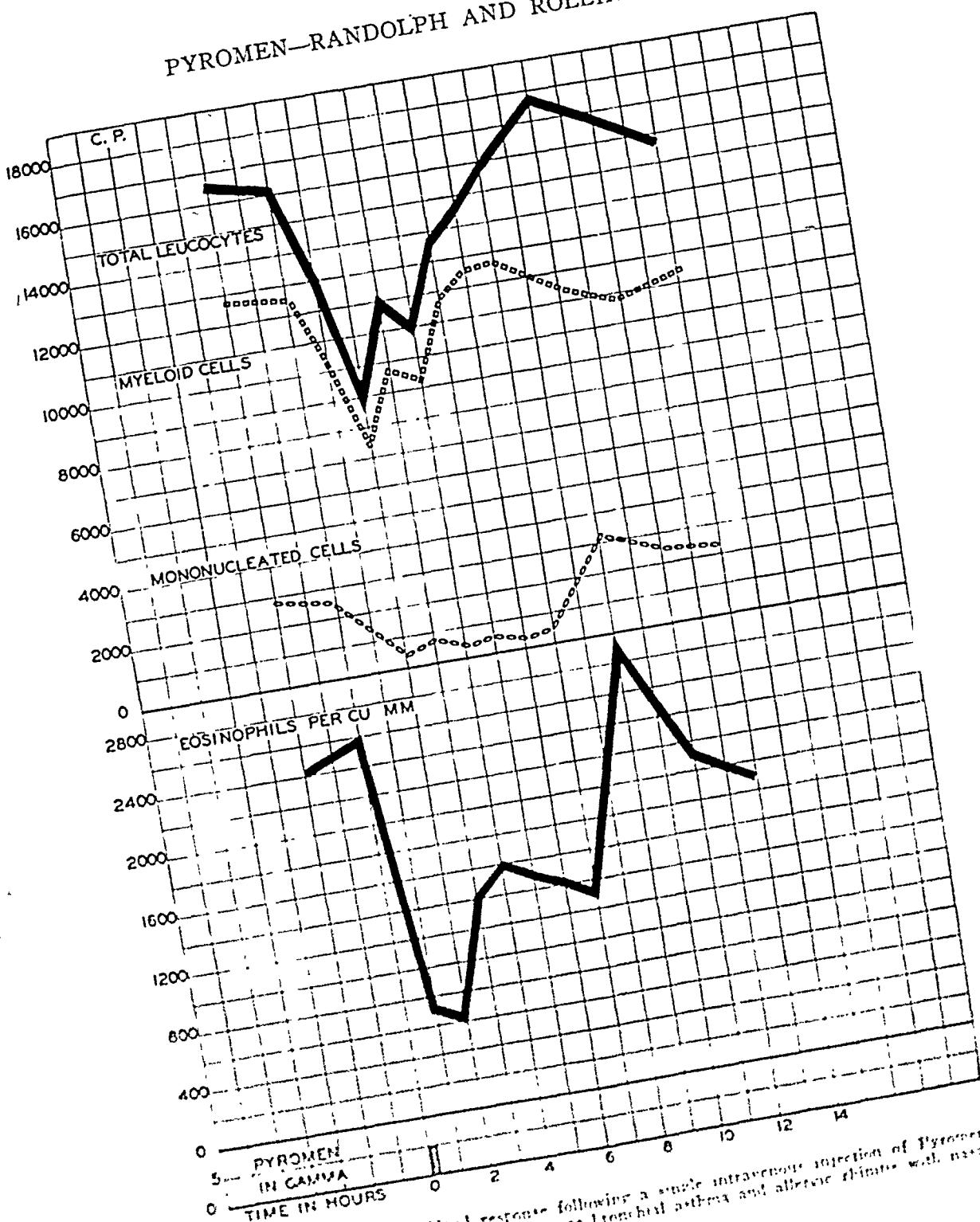
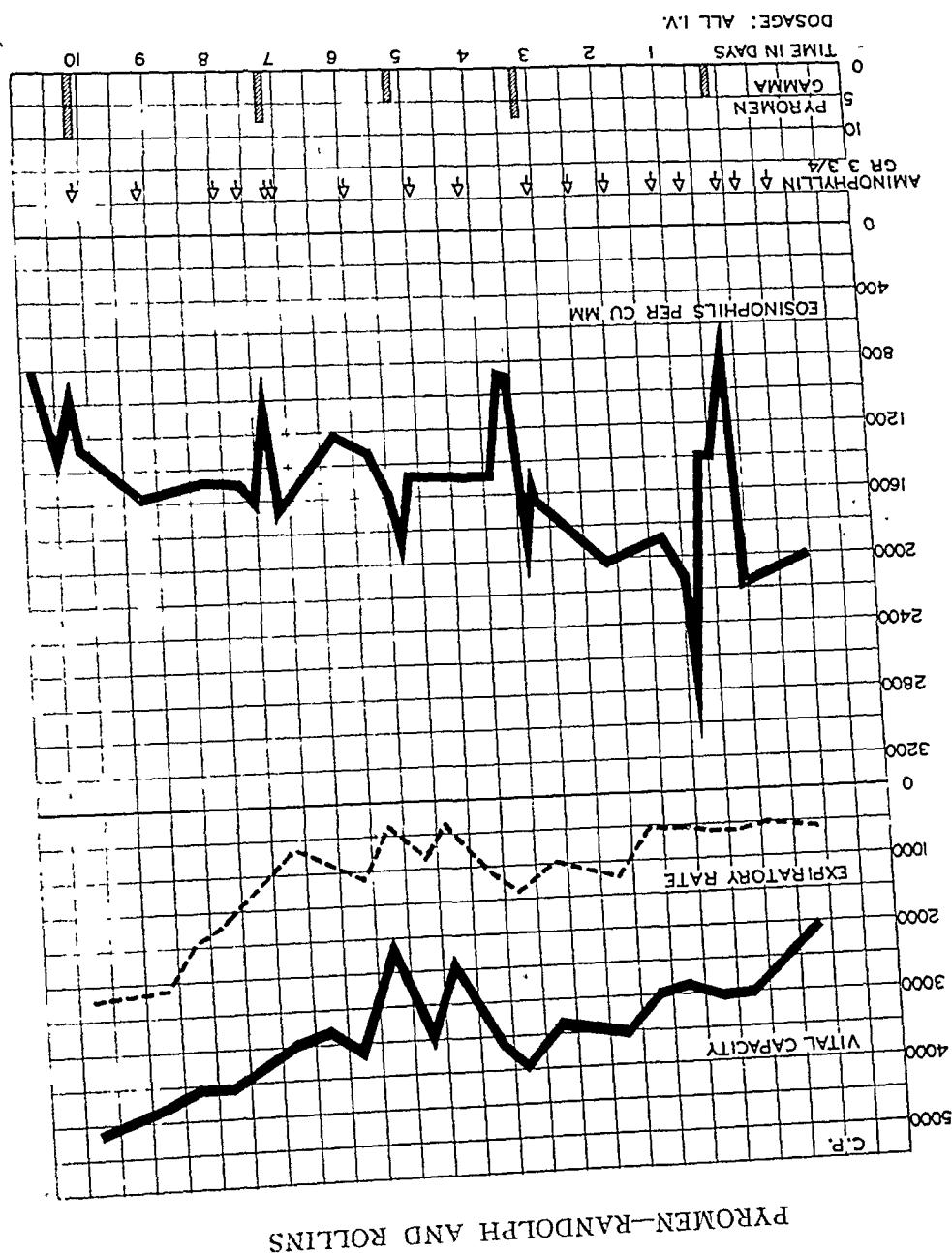


Fig. 1. A characteristic blood response following a single intravenous injection of Pyromen in C.P., a patient with a diagnosis of severe bronchial asthma and allergic rhinitis with nasal polypi.

of effectiveness following the second dose, the interval between these doses usually varying between three and seven days. Fourth and subsequent intravenous injections are administered as often as necessary in order to perpetuate the degree of improvement previously attained. The interval between injections at this stage of therapy usually varies from three days to three weeks, depending somewhat upon the alterna-

manifestation being treated and the individual's specific allergic diagnosis and degree of allergic control. Exceptions to this schedule have been observed in some children in whom beneficial effects may persist for as long as three months. In general, the dosage requirements for children over the age of three years are essentially the same as for adults. Children tolerate the drug well and frequently respond more satisfactorily than adults.

Fig. 2. Variations in the vital capacity, expiratory rate and peripheral blood eosinophilic following a series of intravenous injections of pyromen in C.P., a patient with severe bronchitis and allergic rhinitis with nasal polypi. Similar observations following treatment with ACTH,¹² Cortisone,¹³ and Concentrated Adrenal Extract¹⁴ have previously been reported.



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Variations in the clinical response and level of circulating eosinophils following treatment with repeated intravenous doses of Pyromen is shown in Figure 2; this is the same patient whose blood response following a single intravenous dose was previously illustrated.

In the event the initial intravenous dose is not followed by evidence of clinical improvement, the expected blood response, or by the development of a mild constitutional reaction, a second intravenous dose approximately 50 per cent greater is given at the end of forty-eight hours. Subsequent doses employing the same increment and interval are continued until one or more of the above manifestations of a satisfactory therapeutic response are attained. When an effective dosage level is reached, one determines the duration of the period of clinical improvement by awaiting the recurrence of the former symptoms. If this period of improvement is four days in duration or less, one repeats the former amount in subsequent doses. If this period of improvement exceeds four days in duration and particularly if it exceeds a week, a constitutional reaction may often be avoided by giving a dose 25 per cent smaller than the amount previously administered. This level and interval of dosage may be continued until constitutional reactions occur or until it becomes ineffective; the dosage is then decreased or increased slightly according to the indications. It is sometimes necessary to make several successive step-wise reductions in the dosage in specifically diagnosed allergic patients receiving long-term intravenous therapy, examples of which are illustrated in the upper part of Figure 3. Others, particularly if relatively uncontrolled from the specific allergic standpoint, may often be retained at a constant level or may require a slight increase in dosage; the latter type is illustrated in the lower part of Fig. 3.

Except for patients with specifically undiagnosed dermatitis or bronchial asthma, who appear to require somewhat larger doses, most allergic individuals have been treated within a dosage range of 0.5 to 10.0 gamma (micrograms).

THE ORAL ADMINISTRATION OF PYROMEN

It would appear that Pyromen is absorbed through the buccal mucosa as judged by the development of clinical improvement, the previously described type of blood response, and constitutional reactions following the sublingual use of this preparation. The technique employed is to allow a saline dilution (5 gamma per cubic centimeter) of the material to remain in contact with the buccal mucosa for a period of at least five minutes before swallowing.

In general, a less striking variation in the cellular elements is observed as a result of oral therapy than following the intravenous administration of Pyromen. Comparative blood responses in the same patient are shown in Figures 4 and 5.

The constitutional reactions following oral therapy of Pyromen are

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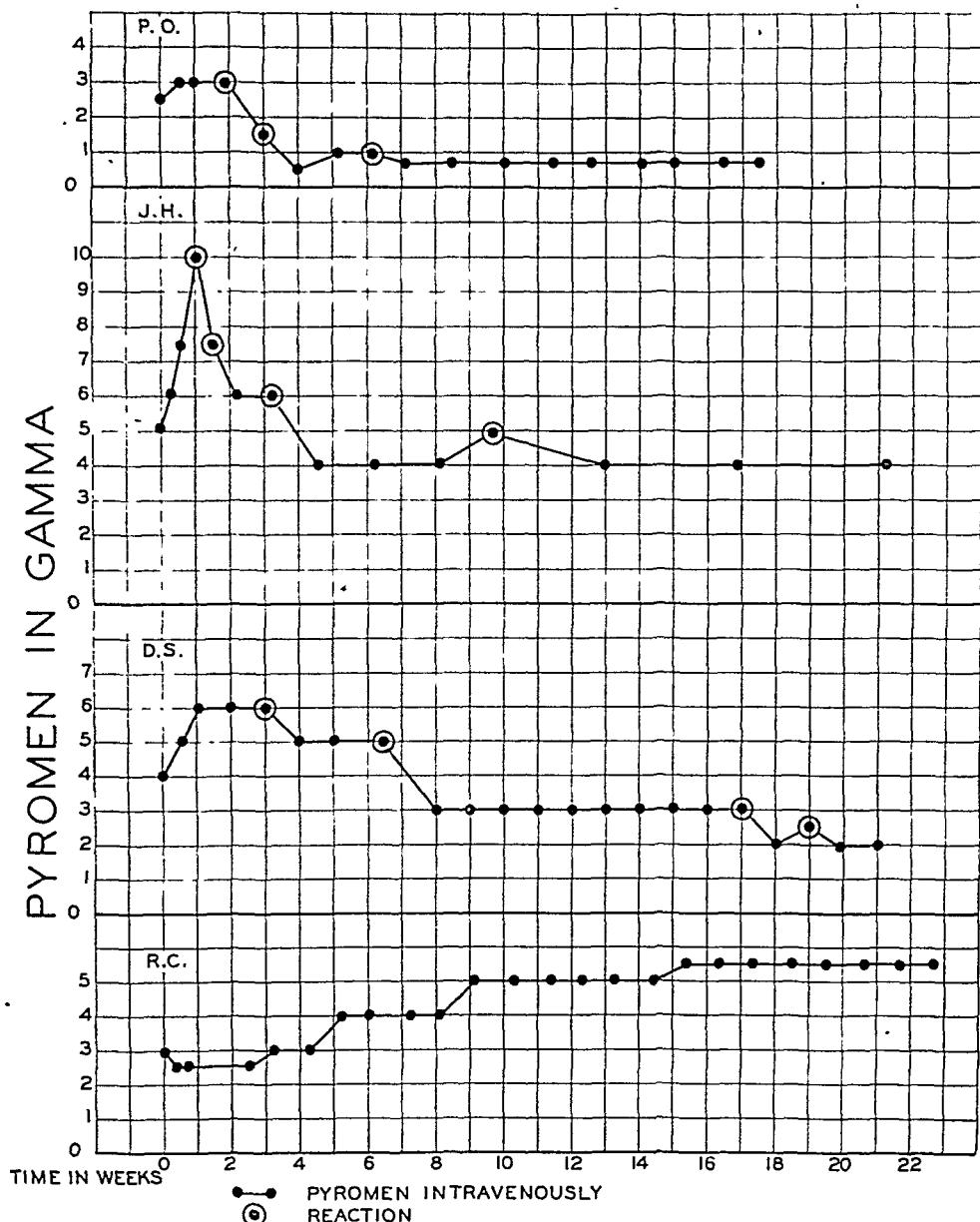


Fig. 3. Illustrative dosage schedules in patients receiving intravenous Pyromen therapy. The first three allergy patients had clinical improvement after the initial intravenous doses shown above but then developed constitutional reactions as indicated by the circles. The subsequent reduced dosages were tolerated and maintained satisfactory clinical improvement. The fourth patient has required a gradually increasing dosage schedule to maintain improvement of her symptoms.

more delayed in onset and less severe than those associated with the intravenous route of administration. The mildest type of constitutional response observed consists of fatigue, irritability, and listlessness developing as late as seventy-two hours after the buccal administration of the drug. This type of response may readily be overlooked unless one is aware of its possible development. With larger doses the reaction

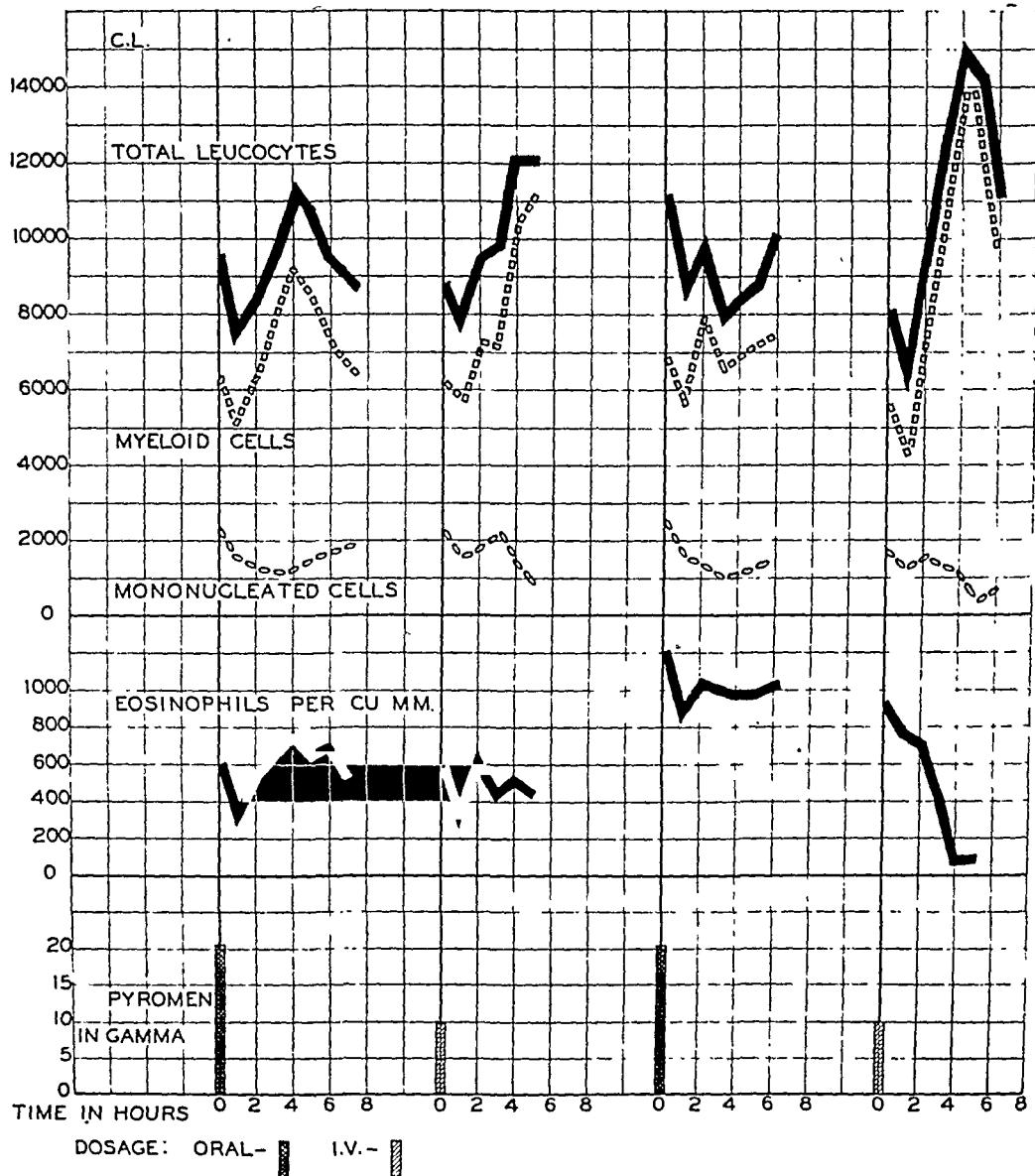


Fig. 4. C. L., a patient with allergic rhinitis, myalgia, and fatigue, had temporary improvement in symptoms following each oral or intravenous dose of Pyromen. Variations in the total leukocytes, myeloid, mononucleated and eosinophilic cells following the alternate administration of Pyromen by the oral and intravenous route are illustrated.

may be expected to come on more rapidly and is usually associated with the additional symptoms of muscle aching and drawing sensations.

Initial attempts to obtain a satisfactory therapeutic response in allergic disease as a result of administering Pyromen only by the oral route have thus far been relatively unsuccessful, although this has been accomplished in several children and occasionally in adults. The oral route of administration has been most helpful when combined with intravenous therapy. A workable joint program consists in giving two to four intravenous doses as previously outlined, following which clinical improvement may usually be maintained as a result of oral therapy. The amount given orally is usually identical or 50 per cent greater than the amount

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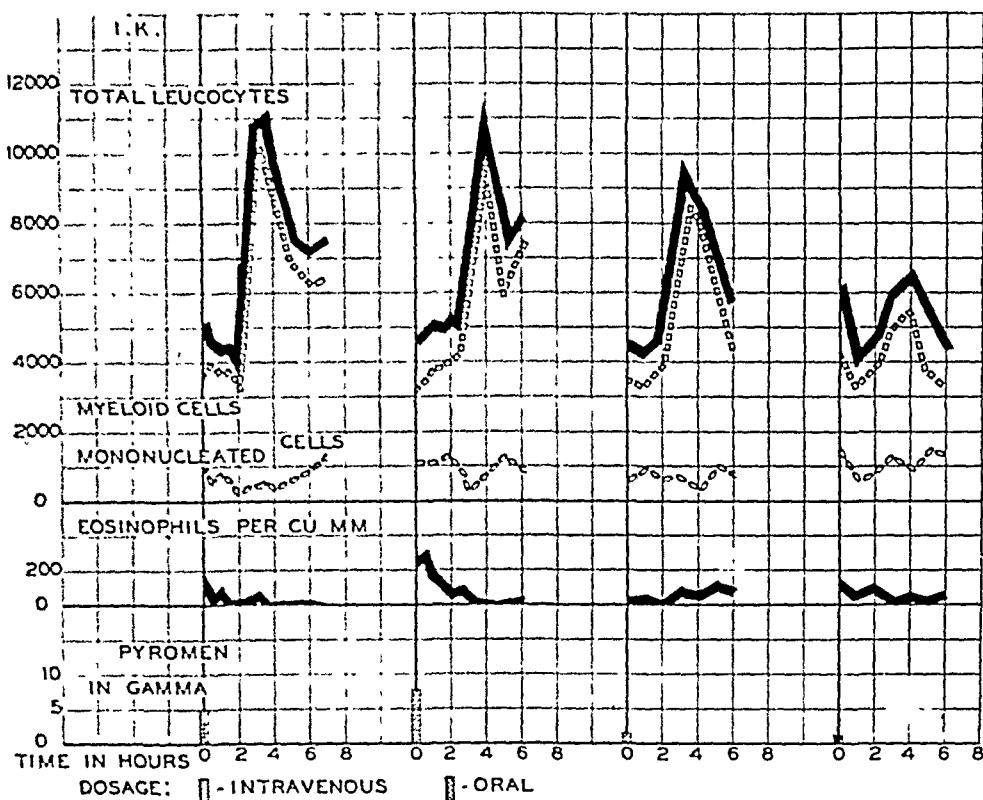


Fig. 5. I. K., a patient with severe allergic headaches, rhinitis and fatigue, whose case report has been published previously,¹¹ illustrates similarities in the blood response with intravenous doses of varying size. When improvement had been obtained as a result of the initial intravenous doses, small amounts administered intravenously or orally were sufficient to maintain clinical improvement.

of the previous intravenous dose; the interval between doses is similar. The clinical effectiveness of continued oral treatment persists for varying periods of time but may gradually diminish after the first month or six weeks. Under such circumstances it is often desirable to repeat one or two intravenous doses, following which oral therapy may again be effective.

As implied, some individuals respond more satisfactorily to oral therapy than others. The range in dosage is quite variable from person to person and considerable time is required to determine the most advantageous dosage level for a given case. Some patients tolerate oral therapy with a highly satisfactory degree of relief of allergic symptoms whereas even very small doses of Pyromen intravenously accentuates their clinical manifestations. As in the treatment of house dust sensitivity,²⁵ some allergic individuals require exceptionally small amounts of Pyromen in order to avoid the accentuation of symptoms and to produce an amelioration of the previously existing allergic manifestations. For instance, in two highly allergic individuals the oral administration of one drop of Pyromen solution containing 5 gamma per cubic centimeter (approximately one quarter of one gamma) has resulted in an

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accentuation of previously existing allergic symptoms and led to the discontinuation of Pyromen therapy. This type of response, however, is uncommon.

It should also be emphasized that much larger doses of Pyromen may be given safely, at least to certain patients, than those recommended in this presentation. Relatively large intravenous doses may often be administered in the absence of severe reactions, particularly in the early phase of therapy, if successive treatments are given at such frequent intervals as once daily or on alternate days. This type of intravenous therapy has not been as effective in our hands as the schedules recommended. If the mechanism of Pyromen action is one of pituitary-adrenal stimulation, as will be subsequently discussed, lower dosage schedules would seem preferable. Once this sequence of oft-repeated doses is broken by several days without Pyromen therapy, it is wise to make a material reduction from the level of the last dose when treatment is resumed in order to avoid the production of a marked constitutional reaction.

In giving relatively large doses of Pyromen orally, one may encounter delayed reactions which are easily confused with apparent "wear-off" effects. When such successively large oral doses are given at frequent intervals, a clinical picture develops of increased general symptoms that is suggestive of the prodromal symptoms of influenza or the exhaustion phase of the alarm reaction as described by Selye.³⁷ However, it is freely admitted that the correctness of this interpretation is somewhat speculative at present. In fact, our present concepts of dosage are by no means final, and the currently recommended schedules may undergo considerable modification with further experience. It is of interest that we have become increasingly conservative in the direction of giving smaller doses at more infrequent intervals as our experience with this agent has increased. This conservatism has not resulted because of the fear of larger doses but is due to the appreciation of superior results obtained from the administration of the smallest dose in an individual case which will bring about effective relief of symptoms with minimal side reactions, and usually in the complete absence of such constitutional symptoms. This dose is then repeated at an interval just sufficient to maintain continued clinical improvement. The actual dosage schedule employed in different individuals and at different times in the same individual is highly variable; it not only depends upon the amount of previous therapy in a particular case but also to some extent upon the allergic manifestations presented, the relative degree of specific sensitivity of the patient in respect to his allergens, and probably upon several other factors, which most likely include the current lability of the pituitary-adrenal system in respect to the ease with which it may be stimulated to greater secretory activity.

RESULTS OF TREATMENT WITH PYROMEN

As most allergic individuals with perennial symptoms are sensitive to both inhalants and foods and as Pyromen therapy seems to be less effective in controlling inhalant symptoms than those from food sensitivity, patients allergic to house dust, silk, and other epidermals obtain more satisfactory results if specific inhalant therapy is combined with Pyromen treatment. Inhalant sensitivities have been diagnosed according to Rinkel's serial dilution technique of intradermal testing,^{30,31} and specific treatment has been based upon the administration of therapeutic doses in relation to the individual's measured end-point of skin test reaction.^{25,32} The combined treatment of inhalant sensitivities and intravenous or oral Pyromen therapy constitutes a workable program and results in more effective management of the allergy patient with perennial symptoms than may be obtained as a result either of inhalant management or Pyromen therapy alone.

A number of patients with specifically undiagnosed allergic manifestations were originally started on Pyromen treatment in the dosage schedules previously outlined in an effort to determine the effectiveness of this type of nonspecific therapy. Although many obtained a considerable degree of symptomatic relief as a result of intravenous treatment or the combined intravenous and oral Pyromen therapy, the results were in general less satisfactory than might be obtained from allergic management alone and it was difficult to effect sustained improvement in spite of various attempts to regulate the dosage of Pyromen. The addition of specific allergic inhalant diagnosis and treatment sufficed to bring about satisfactory results in many, but the more difficult cases required a specific food diagnosis in addition. In the latter group it was found necessary to eliminate at least one or two of the major food allergens in order to bring about sustained satisfactory relief of symptoms, even though both inhalant therapy and Pyromen treatment were also continued.

It should be emphasized that those uncontrolled food sensitive individuals who obtained relief of their allergic manifestations early in the course of Pyromen therapy may commonly have a recurrence of at least some of their allergic symptoms after a month or two of this type of treatment, even though combined with specific inhalant therapy. When Pyromen therapy is partially effective in relieving the symptoms of food allergy or when the relative effectiveness of this agent begins to subside, the allergic individual is apt to develop mild and transient reactions following ingestion of his specific food allergens. This has been observed to occur even though the food in question is ingested under correct conditions of testing,²⁷ whereas under similar circumstances prior to treatment with Pyromen the same food produced clinical responses of greater severity and much longer duration.

The advantages of a specific allergic diagnosis, both in respect to

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inhalants and foods, should be apparent from this discussion, for, in general, Pyromen therapy has been found most successful in patients in whom a partial or complete specific allergic diagnosis has been made. It is particularly advantageous where help is most needed, namely, as an aid in handling the problems of food allergy in those cases in which it is difficult or impossible to avoid all incriminated foods. In certain adults and quite commonly in children Pyromen therapy at times relieves the symptoms of food allergy and allows the individual to return to a general diet, but this degree of improvement cannot be expected in all instances. In the majority of cases of food sensitivity treated with Pyromen it may be necessary to avoid one or two of the most highly allergenic foods while continuing the use of other dietary offenders on a rotating, diversified schedule.²⁰. The actual problem in a given case should be appraised on the basis of the degree of sensitivity existing to various foods and the breadth of sensitivity in respect to the number of foods involved by the sensitization process.²¹

There seems to be little difference in the response of various perennial allergic syndromes to Pyromen treatment, with the exception that certain cases of bronchial asthma and atopic dermatitis frequently require somewhat larger doses for optimum effects and in general fail to respond as well as the allergic syndromes characterized by less extensive structural changes. In addition to the usual manifestations of rhinitis, asthma, eczema, urticaria, headache, and gastrointestinal allergy, additional perennial syndromes described under the designation of allergic toxemia^{35,36} or the fatigue syndrome of allergic origin^{15,23} respond most favorably to Pyromen therapy. This condition includes such symptoms as unexplained weakness, listlessness, fatigue, myalgia, nervousness, and mild depression or melancholia.

Numerous patients with one or more manifestations of the fatigue syndrome, which may or may not be associated with more orthodox allergic expressions, have shown a striking response from Pyromen therapy. Certain students, exhibiting chronic listlessness, irritability, and minor manifestations of depression as well as impairment in comprehension in reading, shortened attention span and chronic sleepiness have received particular benefit from treatment with this agent. This has been evidenced by an improved sense of well-being, clearness in thinking, greater ability to do original work, and ability to read more rapidly and with increased comprehension, all of which has reflected in their general behavior and school performance. Furthermore, this response can neither be induced nor maintained as a result of placebo therapy. Similar observations of this type have been made independently by Fitch.⁵

It should be noted that Pyromen has not as yet been employed in the treatment of seasonal hay fever.

UNDESIRABLE EFFECTS OF PYROMEN THERAPY

In occasional instances we have seen some evidence of an increased bleeding tendency, in patients treated with Pyromen. This was first observed in a male patient with peptic ulcer of many years' duration who developed an acute hemorrhage the evening following his second intravenous dose of Pyromen. Further therapy was not attempted. Several female patients have shown some disturbance in their menstrual cycles in that metrorrhagia and occasionally amenorrhea may occur; this is most commonly observed only during the first period of menstrual flow after the onset of treatment. Other bleeding tendencies have not been noted.

Two patients complained of transient rectal tenesmus the evening following each intravenous dose of Pyromen. A few have noticed the onset of herpes simplex shortly after the institution of Pyromen treatment, but this did not recur even though therapy was continued. Two patients with auricular fibrillation developed a more marked irregularity for a few hours immediately following intravenous Pyromen. In general, however, complications have been few and relatively minor.

DISCUSSION

With the advent of the recently accumulated knowledge of the function of the pituitary-adrenal system, it is becoming increasingly apparent that the beneficial clinical effects known to follow vaccine therapy may be related to this endocrine function rather than being explained solely on the basis of the anamnestic response or other immunological interpretations in the formerly limited meanings of such terms.

Evidence supporting the concept that Pyromen stimulates the activity of the pituitary-adrenal system consists of, first, the demonstration of Windle and associates⁴² that the administration to rabbits of small doses of this pyrogenic material produces an hypertrophy of the zona reticularis of the adrenal cortex suggesting acceleration of cortical secretory activity.

Another point supporting this idea is the fact that the administration of a similar pyrogenic material to patients with malignant hypertension is followed by a material increase in the urinary corticosteroid-like substances; this was reported by Corcoran and Page in 1948.³

A third point in the chain of evidence is the marked similarity in the hematologic response following the administration of adrenocorticotrophic hormone (ACTH), Cortisone and Pyromen, although the variations in the peripheral blood following therapy with these agents is not identical. For instance, the eosinopenia occurring after Pyromen is less complete and more transient than that following the administration of ACTH or even Cortisone. However, Pyromen seems to produce a more profound lymphopenia than does either ACTH or Cortisone. In general, these cellular changes are similar to those described by Selye³⁷ in the alarm reaction. Of particular interest to the allergist is the fact that the same

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pattern in the peripheral blood elements is also produced following the ingestion of an allergenic drug¹⁶ or food¹⁸ in a specifically sensitized allergic individual. In fact, the initial transient leukopenia of such reactions has long been empirically associated with the production of allergic symptoms following the experimental ingestion of food allergens.^{18,28,33,39}

A fourth indication that Pyromen may act in a similar manner to ACTH and Cortisone is the pragmatic fact that these agents are beneficial in the treatment of allergic conditions.^{1,26,34} Comparative clinical studies in a small series of allergy patients treated serially with ACTH,¹³ Cortisone,²¹ Pyromen and Concentrated Adrenal Cortex Extract (ACE)¹⁹ indicate that in the dosage schedules employed ACTH is the most effective, followed by Cortisone and Pyromen, with ACE a poor fourth.

Another point suggesting that Pyromen administration is associated with cortical stimulation and that the beneficial clinical effects of Pyromen therapy accrue therefrom is the marked difference in the clinical response from initial and subsequent therapeutic doses. Whereas the initial intravenous injection may bring about an improvement of allergic symptoms for only a few hours, once this mechanism has been adequately stimulated, subsequent therapeutic doses are much more effective.

It should also be emphasized that in the average allergic individual specific inhalant and food management is still the treatment of choice, for in many cases this is a simple, safe, and workable program. This statement is made in spite of the beneficial results of Pyromen and other endocrine therapy and in spite of the fact that thus far we have seen relatively few complications or contraindications from the therapeutic use of Pyromen. In our experience the most satisfactory results in inhalant allergy have been obtained by determining the current degree of specific sensitivity in accordance with the technique of serial dilution testing, and treatment based upon the results obtained therefrom.^{25,30,31,32} Specific food sensitivity is determined on the basis of provocative individual food tests with the most frequently ingested items of the diet.²⁷

The long-term effects of therapy with Pyromen, ACTH, or other similarly acting agents cannot be stated at present. Several allergic individuals receiving continuous treatment for the past eight months are still responding satisfactorily and have not had any obvious ill effects.

SUMMARY

This preliminary report summarizes our clinical experience with Pyromen in the treatment of 150 allergic patients.

Pyromen, a highly refined bacterial product containing complex polysaccharides, evidently exerts its beneficial effect in the treatment of perennial allergic manifestations as a result of stimulating the pituitary-adrenal system. When compared with other agents known to act through this system, it is less effective than ACTH or Cortisone, but nevertheless is a promising agent in the therapy of chronic allergic conditions. It is

particularly helpful when combined with specific allergic diagnosis and therapy. Unlike ACTH and Cortisone, Pyromen is effective when administered orally.

Recommended individual doses of this pyrogenic material vary from 0.5 to 10.0 gamma (micrograms). Within this range of dosage the febrile response is usually lacking.

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(Dr. Randolph)
700 N. Michigan Ave.

TISSUE CULTURE OF BLOOD LEUKOCYTES

(Continued from Page 625)

SUMMARY

What previously had been demonstrated in animals has now been shown to be true in man; namely, that the leukocytes of sensitized individuals are killed *in vitro* by the products of bacteria. The clinical applications of this fact have also been described. It was shown that when patients sensitive to one or several strains of bacteria are desensitized to these strains, their symptoms are usually allayed and their subsequent tests for sensitivity are negative. The effectiveness of the treatment of sensitive individuals was found to be dependent upon the specificity of the desensitization.

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METEOROLOGIC FACTORS IN THE DISTRIBUTION OF POLLENS AND MOLDS

A Review and Geographic Influence

HERMAN A. HEISE, M.D., F.A.C.A., and EUGENIA R. HEISE, M.T.
Milwaukee, Wisconsin

EVERY allergist is familiar with the almost universal complaint, "My asthma is always worse in damp weather," although most patients will admit that they have had relief from the use of steam kettles. This paradox indicates that the patients recognize a certain atmospheric condition which is associated with increased disability and mistakenly blame the water in the air for their trouble.

In the past three years we have been making airplane studies of the upper atmosphere which throw much light on the relationship of the weather to certain allergic disorders. A preliminary study³ revealed that pollen grains and mold spores usually reached their highest concentrations in the cumulus clouds. The most interesting observation involved a day-and-night survey which showed that the maximum concentration of pollen occurred at varying altitudes during the day and night. A typical record of variations showed that the maximum concentration of particles climbed to about 6,000 feet from early morning until about midnight, when the level gradually fell to close to the ground at dawn. These undulations of pollens during the day and night were closely related to other observations. In general the level of maximum concentration was clearly visible either as a layer of haze, or clouds, or, in the early morning as a ground fog. It was also noticed that the air was most turbulent in the clouds, and that the haze or cloud levels marked the dividing layer between the bumpy lower air and the smooth upper air. No turbulence was experienced in or above the pollen- and mold-containing ground fog. Hay-fever victims were particularly miserable while the ground fog lasted and undoubtedly blamed the dampness for their trouble. Also, those who kept their windows closed at this time fared better than those who insisted on having "fresh air."

METEOROLOGIC OBSERVATIONS

Later observations⁴ furnished the clue to the physical factors which are responsible for the vertical pollen and mold migrations. When air temperature observations⁴ were included in the pollen and mold surveys, it became evident that the temperature of the air at various altitudes was responsible for the concentrations of particles at various levels. When the air was warm below and cold above, convection currents carried the pollen grains and spores to great heights, thus decreasing the concentration of allergenic particles near the ground. On the other hand, when the air failed to cool with increasing altitude (negative lapse rate), the upward currents

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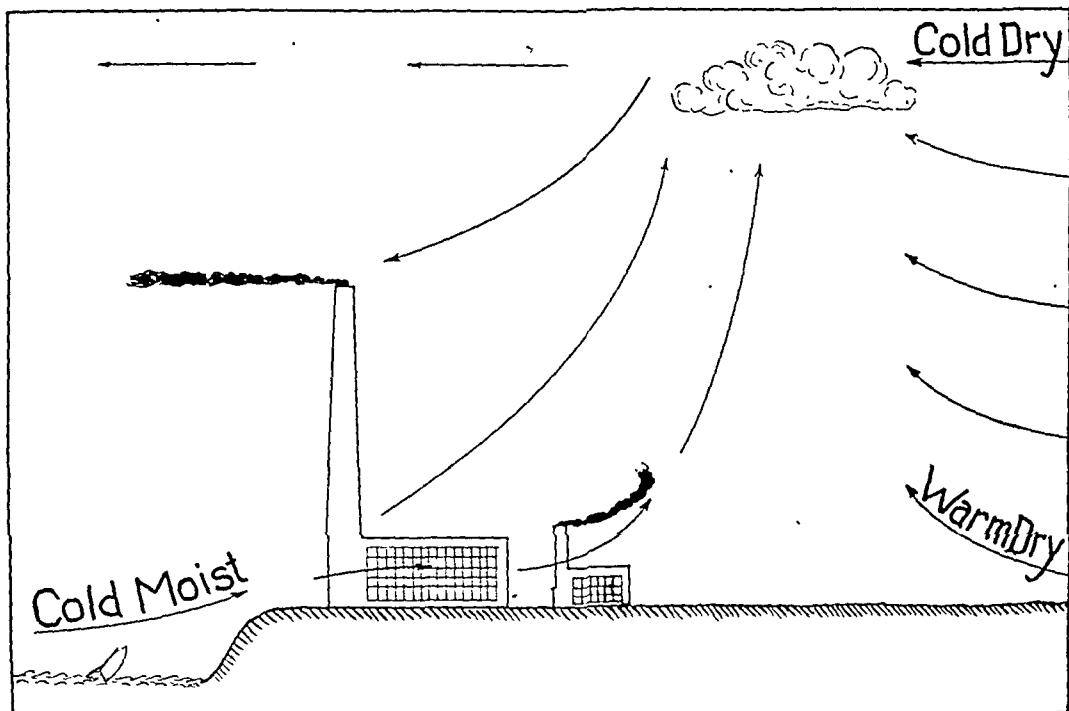


Fig. 1

TABLE I. WEATHER DATA, SEPTEMBER 5, 1948

Madison						Milwaukee					
Time	Ceiling	Visibility	Temp.	Dew Point	Wind	Ceiling	Visibility	Temp.	Dew Point	Wind	
1245	Scattered clouds 5,000 ft.	12	89°	58	ESE 15	Clear	10	80°	66	ESE 13	
1315	Scattered 5,000 ft.	12	89°	58	ESE 15	Clear	10	80°	66	SSE 13	
1415	High thin overcast Lower scattered 6,000 ft.	10	86°	50	ESE 10	High thin overcast	10	81°	66	SE 13	
1545	Scattered 6,000 ft.	8	Missing	Missing	SSE 16	High thin	8	82°	64	SE 10	

ceased and the particles remained concentrated nearer the ground. The worst condition was obtained when in the early morning the ground had lost much heat by radiation while the upper air remained warm (temperature inversion). The warm air, then, overlying the cold layer prevented upward currents. The ground fog results from the cooling of the air near the ground below the dew point.

GEOGRAPHIC FACTORS IN THE DISTRIBUTION OF POLLENS AND MOLDS

Durham¹ has made repeated surveys regarding the geographic distribution of pollens and mold spores. We are particularly indebted to him for his well-known pollen map of the United States. His observation that the west shore of Lake Michigan enjoyed lower pollen counts than regions farther inland, particularly when the wind was from the northeast, has been adequately confirmed. Even with a west wind, the air near the

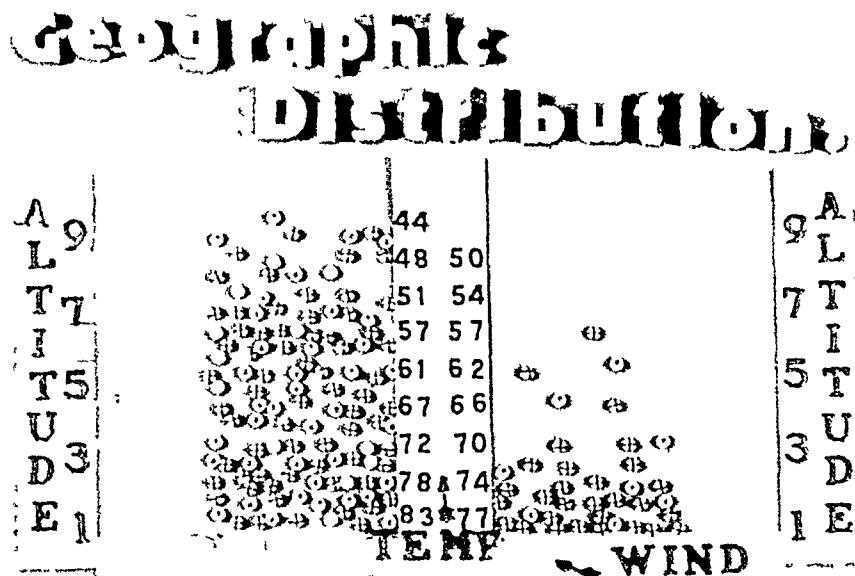


Fig. 2. The numbers at the sides represent the altitude in thousands of feet. The numbers near the center represent degrees of temperature on the Fahrenheit scale. The alternaria spores are shown as dots and the ragweed pollen grains as crosses. The star on the left side of the map represents Madison and the one on the right, Milwaukee.

TABLE II. VERTICAL SURVEYS, SEPTEMBER 5, 1948

	Madison						Milwaukee					
	Altitude ft above sea level	Temp. F.	Smuts	Alt.	Rag.	Remarks	Altitude ft. above sea level	Temp. F.	Smuts	Alt.	Rag.	Remarks
1322	9500	44°	5	30	5	Between clouds						
1330	8500	48°	85	77	105	Between clouds	1530	8500	50°	0	3	3 Clear
1340	7500	51°	165	50	105	Between clouds	1541	7500	54°	0	0	5 Clear
1348	6500	57°	205	10	240	Below clouds	1549	6500	57°	0	6	5 Hazy
1355	5500	61°	220	150	163	Hazy	1555	5500	62°	5	10	10 Hazy
1402	4500	67°	185	105	190	Hazy	1602	4500	66°	10	20	25 Hazy
1409	3500	72°	105	130	150	Hazy	1608	3500	70°	20	20	45 Hazy
1418	2500	78°	165	205	260	Hazy	1618	2500	74°	35	50	135 Hazy
1425	1500	83°	200	160	205	Hazy	1625	1500	77°	175	65	350 Hazy

ground may be moving from the lake to the land, since the heavy colder air from the lake surface displaces the rising lighter hotter air over the ground. The visible evidence of this condition appears when the smoke from low chimneys moves westward while at the same time the smoke from tall chimneys is moving toward the lake (Fig. 1). Another interesting observation is that on a typical summer day when the winds aloft are westerly, the east wind on the surface is noticed for several miles inland. About 10 to 30 miles inland a stationary, narrow cloud gradually forms beginning

METEOROLOGIC FACTORS—HEISE AND HEISE

about 10:00 a.m. and building up till the tops are at times 5,000 feet high with bases at an average of 3,000 feet. These clouds extend parallel to the lake shore, i.e., running north and south. They disappear at about sundown. The practical application of this finding is that most hay-fever sufferers complain of increased discomfort when they are living in the summer resort region which is located 20 to 35 miles west of Milwaukee.

With easterly winds, vertical surveys were made at Milwaukee and Madison. Milwaukee is on the west shore of Lake Michigan while Madison is about 80 miles west. The information of Table II is shown in Figure 2.

An analysis of these data shows, first of all, cooler and more humid air at Milwaukee. The Milwaukee pollen grains and mold spores are few and close to the ground while those above Madison are plentiful and rise to great heights. The reason for this difference is that in Milwaukee the almost pollen free wind which blows over Lake Michigan has too short a sweep to pick up much pollen from the land, while the Madison pollen has been picked up after an overland wind sweep of at least 80 miles.

PRACTICAL APPLICATIONS

Although this survey was limited to the study of solid particles in the atmosphere, it is obvious that the same mechanism applies to the dispersal of gases. During World War I poison gases were found to be most efficient when temperature inversions occurred (warm air above—colder below). Even in times of peace, industries are pouring tons of equally poisonous waste products into the atmosphere with the hope that the wind and air temperatures are favorable for sufficient dilution of the gases to prevent poisoning. However unfavorable weather conditions, such as the inversion which lasted five days in Donora, Pennsylvania, in October, 1948, caused twenty deaths and illness of 5,910 persons—43 per cent of the population.² Those who died were chiefly older persons or those previously suffering from respiratory ailments or cardiovascular diseases. The Donora community also has a high incidence of bronchial asthma.

Knowing under what conditions of the weather particulate matter and gases remain close to the ground in high concentrations, the expression, "My asthma is due to dampness," takes on a new significance.

SUMMARY

Airplane studies indicate that a high lapse rate is responsible for the vertical dissemination of pollen and mold spores, and that a negative lapse rate and particularly a temperature inversion is responsible for maintaining a high concentration of allergenic particles near the ground.

The influence of Lake Michigan on pollen and mold dispersal is analyzed.

The analogy between illness caused by particulate allergenic material and that caused by industrial gases is discussed. Since the most obvious

(Continued on Page 681)

SHORTENING THE TREATMENT OF HAY FEVER

The Combined Antigen-Antihistaminic Technique in Pollen Therapy Study III

A. L. MAIETTA, M.D., F.A.C.A.
Boston, Massachusetts

THE advent of antihistaminic drugs has given a new impetus to the study of allergic diseases. At first, these drugs were employed primarily for relief of symptoms. More recently, a few investigators have suggested their concomitant administration with antigen extracts. Arbesman,¹ Fuchs,² and Green³ observed that sensitive patients could tolerate larger doses of antigen when oral antihistaminic medication was given prior to the injection of the specific antigen. In a group of forty-five pollen-sensitive patients, Maietta⁴ combined progressively increasing massive doses of pollen antigen with a twenty-four-hour simultaneous administration of suitable antihistaminic drugs orally with each injection.

The purpose of this paper is to present a new technique in pollen therapy. The method significantly decreased the number of injections; enabled sixty-five ragweed-sensitive patients to tolerate much larger individual doses than are customarily recommended, conferring upon them a very high degree of protection during the specific season; and produced uniformly satisfactory results.

TECHNIQUE

The sixty-five ragweed-sensitive patients were composed of two groups, a preseasional and a perennial. Thirty patients, presenting themselves for initial treatment prior to the 1949 ragweed season, constituted the preseasional group. Twenty of these who weighed more than one hundred pounds, received eight preseasional, build-up injections of pollen antigen in 250, 500, 1,250, 3,000, 6,000, 10,000, 15,000, and 20,000 PU doses, a preseasional total of 56,000 PU. Ten patients weighing less than one hundred pounds received the same number of injections but with a 50 per cent diminution in the individual doses. Preseasional injections were given monthly, biweekly, weekly, or semiweekly. The pollen dosage schedule was so arranged that the eighth or last injection was given just before the season. Thirty-five patients, having received preseasional therapy prior to the 1948 season, were in the perennial group and were given "maintenance or booster" injections of top pollen doses at bimonthly intervals, six throughout the year. Twenty-two of these had a top pollen dose of 20,000 PU and received 120,000 PU total; while thirteen had a top dose of 10,000 PU and were given 60,000 PU throughout the year. For

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Dr. Maietta is Chief of the Allergy Clinic, Carney Hospital, Boston, Massachusetts; Physician, Winchester Hospital, Winchester, Massachusetts.

SHORTENING THE TREATMENT OF HAY FEVER—MAIETTA

both groups, the Coca-Noon pollen unit, containing 0.00001 mg of total nitrogen, was employed.

A dose of 50 mg of Thephorin was given orally twenty minutes prior to each injection. The injection was prepared by first withdrawing the desired pollen antigen dose followed by 25 mg (1 cc) of aqueous Thephorin,* a new parenteral antihistaminic agent, into the same syringe; inverting several times to mix both solutions; and administering subcutaneously into the arm three or four inches above the elbow. One hour later, a dose of 50 mg of Thephorin was given orally. No other medication was given preseasonally.

In order to expedite the calculations involved and to insure an accurate dosage in the withdrawal of both solutions into the same syringe, an allergy syringe† with a new dual 2 cc calibration was employed. On the right side of the barrel at the distal end, the first cc was graduated in tenths; on the other, both cc in quarters. The dose of pollen antigen, in any dilution, being withdrawn first, was easily measured in tenths; while the required amount of the aqueous antihistaminic preparation was added by utilizing the quarter cc calibration.

RATIONALE

Massive doses or inordinate increments of pollen antigen are likely to produce a constitutional reaction in a specifically sensitive patient. In our study, despite the administration of excessively large amounts of pollen extract, the patients were protected against a severe systemic manifestation by the employment of the combined antigen-antihistaminic technique. It appears that the antihistaminic Thephorin "neutralizes or inactivates" some "general-reaction-producing-substance," probably closely allied to histamine or H-substance, released locally at the site of the injection by the deliberate overdose of pollen antigen. The primary perimeter of inactivation is local, at the site of the injection, where the parenteral antihistaminic, deposited well in advance of the release of the "general-reaction-producing-substance," inactivates the histamine-like substance being released from the tissues. The secondary perimeter of inactivation is in the blood stream, possibly in the immediate vicinity of shock organ cells, where the oral antihistamine, absorbed from the gastric mucosa, is circulating and where any excess of the histamine-like substance, passing into the blood stream from the local reaction, is neutralized.

RESULTS

In the group of sixty-five ragweed-sensitive patients receiving the combined antigen-antihistaminic technique, there were twenty-five males and forty females. Fifty-one weighed more than one hundred pounds, and fourteen weighed less than one hundred pounds. Their ages ranged from

*Supplied by Hoffmann-LaRoche, Inc., Nutley, N. J.
†Supplied by Ecton, Dickinson & Co., Rutherford, N. J.

seven to fifty-six years. Throughout the 1949 ragweed season, the patients received no medication; remained in their usual environment; pursued their normal, daily routine; and did not utilize air conditioning or air filtering units. Each patient kept a clinical diary during the season and tabulated his own results daily. These were graded excellent (completely symptom-free), good (mild, fleeting symptoms during the peak of the season only), and fair (mild symptoms appearing intermittently throughout the season).

Clinical sensitivity to ragweed was established by the history and scratch skin tests with an extract of a 1-50 dilution. The latter were interpreted and correlated in the light of the history. By positive skin tests, twenty-seven patients (42 per cent) also exhibited associated sensitivities to trees, grasses, molds, or house dust. These, however, were unsubstantiated by the clinical history and, for the present at least, were deemed irrelevant.

Side Reactions.—Despite the inordinate dose of Thephorin administered within a relatively short time with each pollen injection, only nineteen patients (29 per cent) complained of side reactions. Insomnia was the most frequent manifestation. Drowsiness and lassitude occasionally occurred also. Side reactions were inconsequential, lasted from one half to two hours and never warranted discontinuance of the technique. Not infrequently, patients who complained of side reactions subsequently tolerated satisfactorily the large dose of antihistaminic medication.

Local Reaction.—Locally, slight itching, burning, or stinging generally accompanied an injection. These symptoms were transient and disappeared within a few minutes. The appearance of the local reaction was delayed from two to four hours in forty-three patients (66 per cent); while in twenty-two (34 per cent) it was evident in fifteen minutes to one hour. Usually the wheal was slight, but the erythematous flare was pronounced. The latter, however, was not always entirely due to the local action of the pollen extract; the slightly irritating effect of the aqueous Thephorin contributed to it also. The local reaction varied from 2.5 to 20 cm in size and lasted from a few hours to as long as thirty-six hours. Associated local tissue edema was proportionate to the size of the reaction.

Post-hyposensitization Skin Tests.—All the patients were retested routinely by the scratch method with a 1-50 ragweed extract within a few days after their last injection and just prior to the ragweed season. The size of the post-hyposensitization skin test was decreased in fifty-three patients about 50 per cent and in four about 25 per cent, while in eight no appreciable difference was noted.

Constitutional Reactions.—In a few patients, previously injected sites flared following subsequent administrations of ragweed antigen. This phenomenon was not classified as a constitutional reaction. Only three patients (4.6 per cent) developed mild, delayed, generalized symptoms consisting of sneezing, pruritus, angioneurotic edema, urticaria, and/or asthma. These symptoms appeared from one to several hours after the injection, lasted from a few minutes to four hours, and were readily controlled with additional oral doses of Thephorin.

In the preseasonal group, massive doses of pollen antigen were administered in rapid progression. Heretofore, these inordinately large amounts were considered inadvisable because of the hazard of constitutional reactions. In this group, two patients developed systemic manifestations. In one, the reaction occurred with the 1,250 PU dose (third injection) and, in the other, with the 3,000 PU dose (fourth injection). In both patients, the remainder of the intensive pollen dosage schedule was decreased 50 per cent. Despite this reduction, these two exquisitely sensitive patients still received high individual pollen doses and a total dosage far in excess of the amount they could have tolerated without the antihistaminic effect of Thephorin.

In the perennial group, (1) top pollen doses were administered instead of the substantially reduced amount of antigen as is customarily done in perennial pollen therapy; (2) the interval between injections was lengthened from the usual three or four to eight to ten weeks; and (3) the amount of antigen, given at a time when the blocking antibody titer was failing, constituted a deliberate overdose from which a systemic reaction ordinarily could develop. In this group, one patient exhibited mild systemic symptoms whenever the top pollen dose of 10,000 PU was administered.

Clinical.—The preseasonal treatment of hay fever for sixty-five ragweed-sensitive patients was shortened considerably and rendered more effective with the combined antigen-antihistaminic technique. Fifty-nine patients (90.8 per cent) had an excellent result and remained completely symptom-free throughout the season; five (7.7 per cent) had a good result and exhibited mild, fleeting symptoms at the peak of the season; and one (1.5 per cent) had a fair result with mild symptoms occurring sporadically during the season.

SUMMARY AND CONCLUSIONS

A new technique in pollen therapy, combining the simultaneous administration of large doses of pollen antigen and an antihistaminic substance, has been presented. The treatment of hay fever has been shortened significantly and rendered more uniformly effective by giving fewer but

(Continued on Page 707)

FATIGUE

M. G. MEYER, M.D., F.A.C.A.
Michigan City, Indiana

FATIGUE merits more medical attention than it receives. Careful surveys of patients are often neglected because, in so many instances, no organic disease can be found. The medical histories of these patients, when carefully analyzed, show that exhaustion to one individual may actually mean constant and severe air hunger, and to the next may only express a willful non-desire to live at the same tempo as his energetically inclined associates.

The material for this paper has been gathered only from those cases in which fatigue is the sole complaint and not an incidental complaint. Three per cent of new patients seen by me over a period of one year have fallen into this category.

The common medical impression is that the great majority of these cases are of psychosomatic origin. Unsolved personality problems; fear states involving physical, mental, or financial security; or an absolutely unreasonable number of hours spent in sustained mental or physical exertion, appear on first contact to offer the most reasonable explanation. I believe, however, with due respect to those dealing in psychological and psychiatric disturbances, that few cases of chronic marked fatigue are ever completely solved by only psychiatric care. The individual today who has no frustrations, no fears, no worries, no religious, domestic, political or employer conflicts, and who has complete harmony with his environment is, indeed, a rare person. Therefore, I feel that all of us have psychoneurotic and psychasthenic tendencies, but I am hoping to find out why Jones, with the same physical status and facing the same problems as Smith, will collapse and seek medical attention while Smith carries on.

This paper was not written with a preconceived idea of presenting it at an Allergy conference. However, I must admit that a certain stimulation came from the following observations. Before anti-histaminic drugs became available, I noticed that hay-fever victims, in addition to their localized rhinitis, complained frequently of utter exhaustion, even though nasal symptoms were well controlled with hyposensitization. This same phenomenon appeared when serum or pollen dosage overstepped the reaction equilibrium. More recently, an interest in food allergy has convinced me still further that the person with an allergic diathesis complains far more frequently of fatigue than do others. Finally, the presence of seasonal variations in cerebral accidents, cardiovascular accidents, musculo-skeletal complaints and psychological disturbances, makes one still more curious about allergic etiology.

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FATIGUE—MEYER

The first fifty consecutive cases with the sole complaint of fatigue are presented in the following charts:

TABLE I. CHRONIC DISEASE ADEQUATE FOR COMPLAINTS

Chronic amebic dysentery	2
Cancer of colon	2
Pelvic inflammatory disease	2
Peptic ulcer with obstruction.....	1
Chronic cholecystitis	1
Rheumatoid arthritis	1
Polycystic kidneys	1
Coronary sclerosis (failing heart).....	1
Hypothyroidism	2
Active pulmonary tuberculosis.....	2
Total	15

TABLE II.
ANALYSIS OF GROUP WITH ORGANIC DISEASE INADEQUATE FOR COMPLAINTS

Anatomical diagnosis	Allergic type with identifiable allergens	Result
Arterial hypertension with early renal failure	2	Dietary exclusion alone—1—well* 1—unchanged*
Early Parkinson's disease	2	Dietary exclusion—1—unchanged Intravenous histamine—1—improved
Asthenia and chronic upper respiratory infection	3	Hyposensitization—2—improved Inhalant avoidance—1—well
Menopause	4	Dietary exclusion—1—well Dietary exclusion and estrogens—1—improved Estrogen therapy—1—unchanged 1—improved
Compensated rheumatic heart disease—previously medicated to compensation	2	Inhalant hyposensitization—1—well 1—unchanged
Pelvic inflammatory disease	2	Dietary exclusion—1—well 1—unchanged till surgery
Total	15	

*"Well" or "improved" refers to "fatigue" only.

Cases well or improved of fatigue by allergic management—48 per cent.

TABLE III. ANALYSIS OF GROUP WITH NO ORGANIC DISEASE FOUND

Functional diagnosis	Allergic type with identifiable allergens	Result
Simple physical exhaustion—Overwork	3	Inhalant avoidance—1—well* 2—unchanged*
Anxiety neurosis and personality disorders	13	Dietary exclusion—4—well 1—improved Inhalant avoidance—2—improved Unchanged with allergy control—2 Psychiatric referral—2—improved 2—unchanged
Migraine—tension headaches	4	Dietary exclusion—2—well Inhalant hyposensitization—1—improved Psychotherapy—1—improved
Total	20	

*"Well" or "improved" refers to "fatigue" only.

Cases well or improved by allergic management—60 per cent.

FATIGUE—MEYER

The number in whom we were unable to establish anatomical or pathological physiological diagnosis is large. I believe that most physicians will agree that this is always true. By the term "allergic type" as used in the tables, I wish to make it clear that I mean those people who gave either a personal history of an allergic reaction or a family history of allergy.

The results indicated are too good. It raises the question of psychic reassurance or the thought that the patient may be carried along by the physician's enthusiasm.

Scientific reasoning for results obtained in this ill-defined syndrome is difficult. I believe one observation is important. People of an allergic type nearly always show vasomotor instability. They blush readily; they show—under stress—erythematous mottling of the neck and upper chest; frequently they have headaches, syncopal-like reactions to powerful psychic stimuli, vertigo, effort syndrome, labile blood pressure, transient paraesthesia and urticaria, and poorly sustained endurance. It is possible, then, that continued insult to the autonomic nervous system by allergens is of sufficient impact to produce fatigue in the same fashion that emotional trauma may produce so-called nervous exhaustion.

Psychologists may well point out that any medical explanation for fatigue is powerful reassurance to the patient, just as is psychotherapy. Yet most have had this treatment. They are, therefore, living in exactly the same environment with only one significant change, and that is the removal of certain inhalants, contacts or foods. If the latter is in itself sufficient psychotherapy, I have wasted your time and mine. For the present I am stubborn enough to hold to my original contention.

DISCUSSION

HAL M. DAVISON, M.D., Atlanta, Ga.—Fatigue is one of the most common symptoms elicited by medical history. Any patient with or without any other complaint and with any type of disease may suffer slight to extreme fatigue. Since physical, mental, and emotional stress all consume energy, it must be assumed that fatigue may occur from causes originating from any kind of stress. Usually, there occurs with all diseases fatigue proportionate to the severity of symptoms or to the seriousness of the pathological processes present, but modified by the individual's resistance.

All patients with fatigue whom we have studied from the allergic standpoint have had one or more proven allergic diseases. In some of these patients there has occurred extreme fatigue out of proportion to other symptoms and for which no other cause but allergy could be demonstrated.

We have been unable to demonstrate that sensitivity to inhalants will be a prominent cause of fatigue, but we have been able to relieve some cases of fatigue by omitting foods from the diet to which the patient is sensitive and able to reproduce the symptom by feeding the patient with these same foods. Milk has been the most prominent offender. We believe that fatigue quite frequently results from sensitivity to foods and that it should be classified as one symptom occurring in cerebral allergy.

I am glad that Dr. Meyer has carried his investigation further and studied patients who have no other symptoms but fatigue.

STREPTOMYCIN BLOOD LEVELS IN RABBITS FOLLOWING ADMINISTRATION WITH AN ANTIHISTAMINE

F. J. MURRAY, BARBARA TAYLOR, and MILTON J. FOTER
Cincinnati, Ohio

SENSITIVITY occurs in patients being treated with streptomycin, and the frequent development of sensitivity or contact dermatitis in nurses administering the drug to patients has been reported by a number of workers.^{1,3,6} Local reaction to aerosol streptomycin has also been recorded.⁷ Antihistaminic drugs have been found of value in controlling some of the skin eruptions and other allergic symptoms resulting from streptomycin therapy.

Simon⁴ has shown the antihistamine Decapryl* (Doxylamine) Succinate (dimethylaminoethoxy-methylbenzyl-pyridine) to be of value in the treatment of penicillin reactions and in the prevention of such reactions. The combination of penicillin and Decapryl Succinate Minergic Solution was reported to result in fewer reactions, to be practically painless on injection and to evoke blood levels comparable to those produced by penicillin alone. In studies conducted on rabbits injected with penicillin and Decapryl we found that the antihistamine had no effect on blood levels.²

Simon has suggested that antihistamines may be of value in combination with other drugs capable of eliciting sensitivity, and it seemed desirable to evaluate the effect of Decapryl on streptomycin and dihydrostreptomycin blood levels in rabbits.

The dosage of antibiotic in our experiments was 50 mg per kg body weight, and all injections were made in the posterior left thigh muscle. Bleedings were by intracardial puncture, and the assay was a modification of that described by Stebbins and Robinson.⁵ The average weight of the rabbits was approximately 2.7 kg.

The antihistaminic solutions employed contained 15 mg Decapryl Succinate per ml, 5 ml being added to 1 gm vials of antibiotic.

The results of blood level studies on streptomycin are shown in Table I. It can readily be seen that levels induced by the combination of antibiotic and antihistamine were as high as, or higher than, those induced by the control preparation.

Table II shows that results with the combination of dihydrostreptomycin and Decapryl are essentially the same as those obtained with the antibiotic in saline.

Differences between median averages at given time intervals are probably of no therapeutic significance, and it is evident from the overall comparisons that Decapryl has little or no effect on the blood levels induced

* From the Department of Bacteriology, Research Laboratories, The Wm. S. Merrell Company, Cincinnati, Ohio.

† Trademark of The Wm. S. Merrell Company.

by streptomycin and dihydrostreptomycin. The results would indicate that Decaprym, whether proposed for prevention of sensitivity to streptomycin, or for concurrent administration when both drugs are required, is not contraindicated by inactivation of the streptomycin.

TABLE I.
STREPTOMYCIN BLOOD LEVELS

	Hours-gamma per ml		
	½	3	6
Decaprym Diluent—Rabbit			
1	99	38	10
2	88	35	7
3	86	38	8
4	86	32	—*
5	92	39	11
6	135	78	26
7	79	29	—
8	82	33	13
Median Saline	85	36	9
9	85	32	7
10	71	36	6
11	76	57	24
12	100	34	12
13	66	32	8
14	68	28	10
15	74	32	10
16	86	32	7
Median	75	32	9

*Level below 7 μ g per ml, approximate limit of assay.

TABLE II.
DIHYDROSTREPTOMYCIN BLOOD LEVELS

	Hours-gamma per ml		
	½	3	6
Decaprym Diluent—Rabbit			
1	110	40	16
2	88	23	—*
3	86	36	—
4	86	41	—
5	94	41	10
6	134	67	29
7	84	21	—
8	74	15	—
Median Saline	87	38	—
9	80	33	—
10	90	27	7
11	81	27	8
12	70	32	—
13	97	32	8
14	102	19	—
15	105	23	—
16	102	23	—
Median	93	27	—

*Level below 7 μ g per ml, approximate limit of assay.

CONCLUSION

Rabbit blood levels achieved with combinations of streptomycin or dihydrostreptomycin and the antihistamine Decaprym were essentially the same as those induced by saline solutions of the antibiotics.

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Lockland Station
Cincinnati 15

NUTRITIONAL THERAPY IN THE MANAGEMENT OF RESPIRATORY, ANAPHYLAXIS OR ALLERGIES

HERBERT N. VERMILYE, M.D., F.A.C.A., Forest Hills, New York
and
MARVIN R. THOMPSON, Ph.D., Stamford, Connecticut

DISCUSSION OF DETOXICATION

AS the preliminary feature of this presentation, we believe that a discussion of detoxication is of prime importance in the over-all contemplation of the broad study of anaphylaxis. The very word, anaphylaxis—from the Greek, meaning backward protection—suggests the deficiency of natural biologic forces, namely, immunogens, antibodies or detoxicants in the organism, essential to combat the invasion of sensitizing agents whether they be undigested proteins, by-products of bacterial growth or decomposition, or other toxic substances.

It has been brought out repeatedly in the current literature that detoxication is a fundamental mechanism to be considered in allergic response to antigenic agents. For example, we have sensitized a group of animals to horse serum. One-half of the subjects receive enzymatic protein digests and vitamins; the others do not. The nutritionally protected group survive with no evidence of tissue necrosis or the Rich anaphylactic lesions while the unfortified animals die with Rich lesions, hemorrhage, edema, thrombosis or collagen degeneration.

It has been hypothesized that if various toxic agents such as chloroform, snake venom, thyroxin or a lethal dose of diphtheria toxin can be oxidized, reduced and excreted as a non-toxic substance, the course of tissue degeneration (histotoxicosis) in disease should be manageable before material destruction or death takes place. This preventive biologic mechanism is accurately termed detoxication. Some outstanding examples of detoxication may be appropriately stated at this time. Pellagra occurs only in subjects suffering a state of protein depletion brought about by toxic destruction of tissue, and cured by nicotinic acid and enzymatic protein digests meeting the amino acid and strepogenin standards specified by Wooley and Peters.^{9,13}

However, pellagra is not necessarily due to a nicotinic acid deficiency *per se*. It may be traced in certain instances to the blocking action of an analog such as 3-acetyl pyridine found in corn. This mechanism is typical of many metabolite deficiencies. The metabolite and its structural analog compete for position in the particular enzyme chain reaction which must proceed normally for metabolic needs. This phenomenon finds a parallel in many allergenic reactions; for example, antigenic agents block metabolites and cause eczema, but when an enzymatic protein digest is introduced in therapy, the detoxication properties of this substance prevent the disorder.

The work of Claussen offers still another parallel. This investigator showed that during infectious periods, the fat and water soluble vitamin reserves were severely depleted. More recently, it has been found that crude liver, folic acid and enzymatic protein digests re-establish assimilation. We are of the opinion that the normal individual in a state of health is equipped to combat most infections. This protective mechanism depends largely on the availability of adequate amino acids, strepogenins and vitamins through the diet and/or medication and the ability to utilize these factors by normal digestive processes. Psychosomatic elements must be ruled out when considering the latter, as fear, worry or tension may interfere with digestion, thus causing nutritional depletion.

It is felt that the development of natural resistance to foreign proteins is purely a problem of biological adaptation to environment. States of histotoxicosis or protein depletion, whether innate or acquired, interfere with the normal process of adaptation. An inflammatory adaptation takes its place and may only be corrected by eliminating the histotoxicosis through the re-establishment of normal amino acids, strepogenin and vitamin levels, and utilization of these agents. This is understandable in the consideration of infants with pancreatic deficiency who show marked deficiency in all the oil soluble vitamins, fail to grow and frequently go into hypocalcemic tetany because of vitamin D deficiency. These infants are anemic and are subject to colds and staphylococcal infections. We find that when treated with pancreatin and enzymatic protein digests these infants grow and gain weight rapidly. All this further emphasizes the importance of considering the action of toxins, both endogenous and exogenous in the study of disease and the necessity for regarding nutritional enzyme systems as detoxifying influences as well as basic material for new cellular replacement and growth.

ANAPHYLAXIS IN THE BROAD CONCEPT

Inability to utilize normally the basic nutritional factors constitutes a fundamental defect in those of so-called allergic constitution. In these patients, sensitizing antibodies are present in the organism instead of natural factors of resistance. It must be stated that a natural resistance to an infection or an antigenic invasion, implies a cellular state existing without injury in a toxic substrate.

The untreated patient in most instances shows a persistently negative nitrogen balance brought about by uncompensated toxic protein loss. These patients, in a state of suboptimal nutrition, demonstrate characteristic manifestations of allergic response to antigens, namely, Rich lesions, Schwartzmann reactions, hypermotility of smooth muscle, increased susceptibility to Gram-negative bacterial invasions with penicillinase resistance to treatment with penicillin. The latter may be attributed to the fact that in the state of suboptimal nutrition common to the allergic patient, peni-

cillinases are produced sufficient to inhibit concentrations up to 800 units per ml. Thus it becomes necessary to treat these patients successfully with other antibiotics such as Aureomycin for example.

All this has been explained in terms of toxic protein loss; in treating these patients, it is not sufficient to attempt bringing about an adaptation to a faulty biologic environment by elimination diets, desensitizing treatment schedules and symptomatic drugs such as aminophylline, theophylline, sodium glycinate, phenobarbital and belladonna. It is of supremely greater importance to institute a rich nutritional schedule using intravenous amino acids and plasma. In dealing with the constitutionally allergic patient, shock tissue is not confined to the bronchioles and the alveoli. The heart, liver, skin, gastrointestinal tract, in fact, any part of the entire organism may be involved. In the treatment of these patients, we proceed conventionally at first, providing symptomatic relief, as well as attempting to condition the patient to the abnormal biologic environment inherent to the allergic individual. Upon simultaneous administration of intravenous amino acids and oral enzymatic protein digests, we are able eventually to place the patient in a state of nitrogen balance, arresting and even reversing the toxic protein loss, provided we employ salines and plasma infusions according to the technique of Barclay Parsons along with symptomatic treatment (aminophylline gr 7½; phenobarbital gr 2½; epinephrine 0.3 cc).

Upon the achievement of this objective, the so-called allergic constitution becomes a somewhat less difficult problem. Sensitized tissue becomes more readily desensitized. Degeneration, due to anaphylaxis, is prevented by the better ensuing nutritional status of the patient.

We are able to point to patients originally diagnosed generally allergic and who with a persistent infection, when treated as described, emerge as different individuals. As their infections come under control, the allergies become less manifest and more readily manageable. Hyperergic skin tests become completely negative after the optimal nutritional state has been achieved. The patient may become freely exposed to pollens or ingest foods to which he was highly sensitized and which before nutritional treatment would have precipitated a marked anaphylactic reaction and even death.

It is interesting to note, too, that the allergic patient untreated nutritionally shows a marked lack of resistance to bacterial infections; these individuals display a high incidence of sinusitis, pneumonia (all types) and other states often ineffectively treated with antibiotics because of prevalent histotoxicosis.

But how about "non-allergic" patients brought into a state of malnutrition from conditions such as severe infections, diabetes mellitus, hepatitis, pregnancy, liver cirrhosis, burns, overwork, alcoholism, et cetera? These subjects, too, show many of the symptoms and stigmata char-

acteristic of the true allergic. They all suffer a severe toxic loss of protein frequently with increased susceptibility to infection, hypermotility of smooth muscle, hypersecretion, Rich lesions, Schwartzmann reaction, edema and asthma.

Until toxic loss of protein is checked with enzymatic digests* (both oral and parenteral) blood plasma injections and accompanying vitamin therapy, if necessary, an anaphylactic state persists with an increasing involvement of the entire organism as shock tissue. Nitrogen balance is the goal in these cases and not until accomplished is control established.

We have treated patients who have been referred for psychiatric management. A female in particular was relieved by aminophylline parenterally ($7\frac{1}{2}$ gr). With the removal of a tooth and subsequent treatment with penicillin and streptomycin, allergy to house dust disappeared. This was only transitory however; three years later, severe asthma returned soon after a fractured arm was sustained. The nutritional status was so poor that it took six months to effect union in the fracture. Many cases of "invalidism" begin with the inability to maintain nitrogen balance. Acquired allergies and mold infestations so prevalent in these conditions are due primarily to nutritional failure. Many of these patients show characteristic reactions to house dust and ragweed, but are free of symptoms until nutritional failure due to surgery, infection or fracture, intervenes.

According to M. B. Strauss,¹² pregnancy toxemias are due in great measure to diets low in protein. By establishing biologic balance, thus checking protein loss, we are able to prevent convulsions, cut down edema and reduce to normal, hypersecretion and hypermotility of the smooth muscle. Of special consideration in nutritional failure, incident to pregnancy, is the frequency of anemia. Blood dyscrasias of particular gravity are of the macrocytic type. We are able to find no incidence of obstetrical anemia when the daily intake of protein approaches a value of 75 gm daily. Often, it becomes impossible to provide adequate protein needs through dietary sources alone. Co-Tui has stated that pregnant women with pernicious vomiting were better able to tolerate oral protein hydrolysate than natural foods.

The pediatrician too, as attested by Hill,⁵ Olmsted,⁸ Hartman³ and many others, finds that hydrolysate substitution and boosting in milk feedings re-establishes the integrity of the skin, and by aiding the development of natural resistance generally alleviates the allergic syndrome in infancy. Children in a state of toxic protein loss often show sensitivity to penicillin. The increase of protein intake to 5 gm/kg per day, with protein hydrolysates, has been preeminently successful in decreasing this sensitivity as well as alleviating, even curing the stubborn sinusitis, hay fever and other urticarial manifestations of sensitization.

*Protein Hydrolysate-MRT for oral use employed in our studies

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That the nutritional state of the infant is of profound importance in explanation of ability to combat infection, is shown by my patients, identical twin girls, living together, with marked difference in resistance to disease.

Their mother who gave positive skin tests to feathers, spring grasses, house dust and ragweed was cured of relapsing bronchitis. After treatment for a type 111 pneumococcus pneumonia with 100,000 unit doses of penicillin every three hours parenterally, combined with aerosol and aerosol suction, she lost both her clinical and skin tests to allergies.

Twin A ate well all foods, especially meat; refused all vitamin therapy and had no illnesses. Twin B received Vitamins A and E (Claussen) and Procholon to stimulate her appetite and for protection, in spite of which she contracted all diseases to which she was exposed. Both twins were nervous but with adequate diets their behavior reactions to medication became better than the average.

In the past three years, Twin B had many streptococcic and pneumococcic infections with hyperemesis, otitis media, sinusitis, tonsillitis, measles, mumps, scarlatina, rubella and pyelonephritis. During these illnesses of Twin B, Twin A took only 1 teaspoonful of sulfadiazine with sodium lactate each day, as a preventive measure, and showed no signs of infection.

When the above infections were cured in Twin B she was put on protein hydrolysate, pancreatic crystals and pancreatic capsules with bile acids, Folvite, and gamma globulin (2 cc a week). Vitamin therapy of all kinds was discontinued. She developed an appetite and intake as good as that of Twin A. For the past year there has been no illness. Her growth is now greater than Twin A.

In general, upper respiratory conditions, including rhinitis, bronchitis, sinusitis and the like, either of allergic etiology or not, all show toxic protein loss. Whether or not the active infection is due to the hypoproteinemia associated with allergy or to the toxic protein loss brought about by bacterial invasion or fracture, is not the main issue. In either instance, we must administer antibiotics such as aerosol or parenteral penicillin, streptomycin, sulfonamides, Aureomycin and Chloromyctin as well as persist in our efforts to achieve a state of optimal nutrition in our patients with intravenous amino acids and oral protein digests.

In treating respiratory disease, we must forever be conscious of this concept, often neglected in general practice. Certainly, penicillin and other chemotherapeutic agents are successful in the nutritionally depleted patient—but only up to a certain point. Get that patient in nitrogen equilibrium by checking histotoxicosis! Not only will the entire antibiotic value of the drug be realized, but the patient will be equipped to combat the frequent recurrences so often encountered in the chronic sinus and rhinitic patient. We have proven this over and over again in our own

practice. It is our observation that patients in a sound nutritional state do not develop sensitiveness to penicillin or become penicillin-fast because of penicillinases; furthermore he does not demonstrate the characteristic urticaria and/or angioneurotic edema associated with an allergic disturbance. It may be appropriately stated that chemotherapeutic agents introduced into the nutritionally adequate patient are free to act antibiotically and not antigenically.

Surgical patients, both preoperatively and postoperatively, are invariably in an anaphylactic state. Admitted to the hospital, they have often used up all reserves, showing suboptimal nitrogen levels which cannot be re-established by even generous diets. Mulholland,⁷ Stengel, Ravdin,¹⁰ Co-Tui,² Davidson¹¹ and others have reported on the necessity of taking these facts into consideration in the medical management of the surgical patient and have recommended intravenous amino acids, oral hydrolysates and often therapeutic vitamin therapy as well, before and after surgery such as gastrectomy, cholecystectomy and herniotomy. They report shortened convalescence, improved tone, increased resistance to infection, disappearance of edema and quick promotion of gastric emptying time. Surgical shock or injury may account for the loss of 20 to 40 grams of nitrogen daily (1.5 to 3.0 pounds of tissue) due to toxic destruction of protein.

We have observed on the Surgical Metabolism Ward at Presbyterian Hospital, that by using shock therapy and oral hydrolysates* equivalent to 85 grams of protein daily, even the initial three days of toxic protein loss, which Peters has stated was inevitable, has been averted. Barclay Parsons believes that toxic protein loss as manifested by surgical shock may be entirely eliminated by these measures despite the ideas of Peters who has preached a doctrine of "let nature take its course."

Relative to the nutritional concept in practice, it is thus seen that there are two prevalent schools of thought. According to Peters, the nutritional status of the patient, brought into negative balance through surgery, infection or whatever cause, will right itself as a matter of incidence after a return to normal status. On the other hand, we of the opposite school have observed that this concept is fallacious. If something is not specifically done about the toxic protein loss, patients are never given a chance to recover. There is persistent retarding of the patient's ability to combat infection; sensitization is acquired instead of natural immunity with resulting disturbances ensuing, prominent of which is respiratory anaphylaxis. Toxic loss of protein sets in after an operation and after struggling to keep alive at a daily occupation for five years or more, cardiac, liver and/or kidney function often shows progressive failure.

We have found repeatedly that these patients do not respond to the

*Protein Hydrolysate-MRT

so-called adequate diet—the beefsteak of Peters so to speak; they cannot eat in the hospital two or three weeks postoperatively and continue to half-live in a state of negative nitrogen balance for years attended by chronic and persistent infections.

This picture is changed with today's accent placed on therapeutic nutritional measures as described to check toxic protein loss.

The application of complete nutrition to surgery is not simple; it involves the consideration of the following factors: optimal weight of patient, observed weight, plasma protein, plasma albumin, plasma volume, nitrogen intake and output.

The orthopedic surgeon, too, is becoming nutrition conscious. Howard⁶ and his associates at Johns Hopkins, in his studies of nitrogen balance during fracture convalescence, found that the human with fracture suffered a markedly increased catabolic rate resulting in large losses of tissue even though the diet supplied theoretically ample protein. A fractured tibia ingesting 120 grams of dietary protein could not maintain nitrogen equilibrium; he lost about 200 grams of tissue nitrogen during the first thirty days after injury. We must remember that bone is laid down over a protein foundation, and that this stroma must be repaired before bone is actually regenerated. Hypoproteinemia thus interferes with fibroblastic repair and also tends to reduce serum calcium because half the serum calcium is bound to serum protein.

The nephritic and nephrotic patients present invariable signs including tissue depletion, hypoproteinemia, proteinuria, hypertension, hypermotility of smooth muscle and hypersecretion. With blood levels falling to 2.5 per cent for albumin and 5.5 per cent total protein, edema appears and progresses as values fall still further. We find that intravenous feedings and enzymatic yeast digests elevate protein values with great rapidity.

Medical literature describes at length heart abnormalities closely associated with nutritional failure and the converse. The so-called "Beriberi heart" is not a manifestation of mere thiamine deficiency, but of the entire B complex, amino acids, et cetera. Youmans¹⁴ states that protein deficiency brings about dyspnea, lessened blood volume, and finally actual loss of heart muscle substance. Bradycardia at rest is observed in more severe cases and, with hypothermia, hypotension and low metabolic rate, usually goes along with a state of malnutrition.

Other clinical pictures faced by the cardiologist such as congestive heart failure, coronary insufficiency, acute coronary thrombosis, active carditis, or circulatory shock are closely allied with failure in intermediary metabolism. From this metabolic failure, anoxia causes retardation of tissue oxidations because of important co-enzyme destruction. Pyruvic acid metabolism becomes defective; the extent of pyruvemia is a measure of the degree of heart failure. Hermann states¹⁴

"Feeding of high protein, acid or neutral ash, as well as sodium free diets are indicated in most patients with congestive heart failure and edema. Proteins of good biological character may be supplemented with protein hydrolysates, amino acids, yeast or choline."

Good nutrition is an important phase for the clinician to consider in attempting fortification and therapeutic support to compensate for the defects of intermediary metabolism in the cardiac patient.

Of the allergic patient in cardiac failure, we can say the heart is shock tissue with the anaphylactic symptoms described in terms of the foregoing and identical with them. Whether or not the cardiac involvement is an outgrowth of an allergic constitution or brought about by infection, renal failure, fatigue or any cause whatever, we find that these patients respond to therapeutic nutritional measures as described. True, we treat these patients symptomatically and palliatively with digitoxin, aminophylline, barbiturates, et cetera, but if we hope to arrest the degenerative process, yes, even reverse it in certain instances, the nutritional attack is the only measure of true curative significance.

We can discuss virtually every medical problem in the light of the foregoing—namely, that of anaphylactic shock brought about by toxic protein loss, liver cirrhosis, burns, peptic ulcer, diabetes, geriatrics, alcoholism, dermal dyscrasias, certain hearing and neuropsychiatric disorders.

The main attack in anaphylaxis is nutrition—dramatic therapeutic nutrition. Of most importance are intravenous hydrolysate feedings supplemented with enzymatic protein digests from yeast which contains the streptogenins stressed by Woolley to be of great significance. The development of quick protein levels at the beginning of treatment in severe anaphylaxis, by parenteral administration of blood plasma, amino acids or hydrolysates, may be mandatory.

Peters of Yale takes considerable issue with us on my somewhat emphatic insistence on the use of hydrolysates as the preferred source of protein in these cases. Peters has stated that beefsteak or an equivalent dietary protein source is just as good, if not better; moreover, it is cheaper and considerably easier on the digestion and palate. Peters claims that only in the exceptional case is the employment of an amino acid injection or a protein digest necessary and therefore advisable.

We believe that Peters has failed to take into consideration the fact that in patients of allergic disposition, more often than not, whole protein is difficult if not impossible of digestive breakdown. This introduces the constant hazard of whole or partially digested protein entering the organism, augmenting the anaphylactic state or even precipitating further attacks.

And what about these patients with pancreatic, liver, and gastric dysfunction brought about through malnutrition, alcoholism, cirrhosis,

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pregnancy, ulcer and a host of other conditions? These patients need protein, but in many instances cannot obtain their requirements from the dietary no matter how rich, due to reduced pancreatic function often present.

CONCLUSIONS

In conclusion, let us state that the anaphylactic state commonly associated with those of so-called allergic constitution cannot truly be differentiated from shock as observed, in the many phases of medical practice enumerated in this paper. They all are characterized by toxic loss of protein (histotoxicosis), hypermotility of smooth muscle, hypersecretion and the involvement of any organ of the body as shock tissue. And anaphylaxis in the broad sense can be managed in the true curative manner only by the use of true therapeutic nutritional measures, the more prominent of which are intravenous feedings of protein hydrolysates or amino acids supplemented by oral digests and vitamins if necessary.

We may also add that with the acquiring of positive nitrogen balance, there is virtually no digestive disturbance, sensitiveness to penicillin or other potential antigens. These factors are readily neutralized and eliminated by an actively functioning liver. The mechanism of detoxication by amino acids is so important during all phases of living that we may conclude that many of our important enzyme systems lose their important vitamin components during periods of negative nitrogen balance. We should also reaffirm that in the bringing about and maintenance of positive nitrogen balance, the most dramatic observations are at hand with intravenous therapy.

Sometimes, one or two intravenous feedings will accomplish more than it would seem possible from the relatively small amounts of protein-vitamin introduced into the circulation. After one such feeding, a patient, often with poor appetite, is able to maintain nitrogen balance by diet alone. Anorexia, in the surgical patient, for example, is often overcome in a matter of twenty-four hours. This very same anorexia after illness and surgery, customarily seen in the hospitalized patient, may persist for five to ten years with developing hepatitis and marked by negative nitrogen balance and a state of chronic infection characteristic of the malnourished. Again the answer here is nutrition as described, along with the program advocated, employing symptomatics and antibiotics as indicated.

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Herbert N. Vermilye, M.D.
74 Ascan Avenue

BRONCHIAL ASTHMA IN SMALL COMMUNITY HOSPITALS

(Continued from Page 621)

1. A thorough allergy survey to include history, family history, x-ray examination, and laboratory examinations for eosinophiles in the blood and in the nasal secretions.
2. Preventive treatment, skin tests, avoidance and elimination of offending allergens and education of patient and doctor in the widespread incidence of asthma.
3. Specific desensitization.
4. Judicious and proper use of drugs of choice in the acute attacks with a specific warning against the use of narcotics.
5. A well-equipped, air-conditioned, air-filtered asthma room in every hospital.

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THE APPLICATION OF PSYCHODYNAMIC CONCEPTS IN AN ALLERGY PRACTICE

BENNETT KRAFT, M.D., F.A.C.A.
Indianapolis, Indiana

IT is now generally agreed that the conditions we are called upon to treat cannot all be explained in their entirety on an antigen, antibody basis, nor can they all be treated successfully immunologically or pharmacologically alone. It is also generally accepted that emotions, such as anger, hostility, envy, or guilt, can produce specific physiological changes which either may set in motion allergic symptoms or protract or prevent recovery from them. I believe that in the majority of patients we see it is not a question of *either* allergic or psychosomatic but *both* allergic and psychosomatic, since both psychological and allergic factors can play a part in the cause and influence the course of the diseases we are treating.

The terms psychosomatic and psychodynamic are new, but what they describe is not. It has always been known that we blush with embarrassment and get pale with fear, that feelings are accompanied by certain physiological changes, neurovascular in nature, which can be observed objectively. Primitive man had to fight in order to live, and when outnumbered or confronted by greater strength, had to, and did, run. This "fight or flight" mechanism is still with us, in spite of the fact that we do not always fight or run when confronted with obstacles. In the face of danger to the organism, the vegetative functions prepare for "fight or flight." In persons suffering from neurotic conflicts, normal expression of certain emotions is blocked because of repression and inhibition, resulting in chronic emotional tension with ensuing disturbances of the vegetative nervous system.

In the last few years, I have tried to evaluate and treat both the allergic and tension components in my patients; and this paper is an attempt to discuss the new orientation I had to acquire before I could do so.

Regardless of the psychopathologic school to which one adheres, the fact remains that each psychosomatic reaction encountered is the end result of an individual's attempt to meet some life situation.

The first adjustment I had to make was in the taking of the history, because many facts about the patient's past and present life situation, which previously did not seem important to me, now assumed great importance, since they gave me an idea of past patterns of behavior. I also had to learn that what the obtained data meant to the patient or how he felt about them was the most important question. What emotions did the patient show when he talked about his parents, husband or wife, sisters, brothers, or employer?

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The second thing I had to realize was the fact that to be sick means to be dependent on others and that a patient's relationship to the doctor is not like that of one adult to another, but more like that of a child to a good parent. Therefore, just being the kind of doctor who understands those dependency feelings will help the patient. That the physician's personality is an important therapeutic tool with which he works has long been known. However, since we are dealing with the patient's feelings, the first and most important requirement for the doctor is to be objective about his own feelings. If the doctor himself is a rigid person and is unable to be objective about his own emotions, he will not be able to help these patients, because he will be hypersensitive or blind to those things in the patient which he has repressed within himself. This may explain why one physician can help certain patients while another may not.

The third point I had to realize was that we do not change a patient's feelings by reasoning with him—there is nothing logical about emotion. We do help him, however, if we accept his illogical emotions as his right and dilute them by helping him realize that many others would feel the same way under similar circumstances.

The question is frequently asked—"How does one get a patient to talk freely about his troubles and innermost feelings?" As to this I would like to quote Dr. Thomas Rennie, Associate Professor of Psychiatry at Cornell University:

"The method to be used is not one of digging for confessions or striving for a complete history such as you might obtain by following an outline. The method is that of creating a special situation in which the patient feels that he is understood, that he has time to talk, that the doctor really hears what he is saying, that he can talk about many personal matters that he has had no previous opportunity to bring out, knowing that his story will be respected as valid material worthy of a doctor's time and interest. That objective, of course, is best attained by creating a sensitive, understanding atmosphere which permits such material to emerge spontaneously from the patient; consequently, the patient will do most of the talking and the doctor will do very little of it, if he is a wise physician. The patient, like everybody else, is seeking a human being who understands him, a human being who stands behind him ready to support him and encourage him and give him insight and understanding. In the wise doctor he finds a human being to whom he may go with his problems, a person who understands and protects him and has a nonpunitive attitude toward him, and who gives him, primarily, the opportunity to talk and talk and to get out of his system many of these emotional matters that he has previously kept bottled up."

Quite often, and especially with patients who do not talk readily, a

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very helpful procedure for the detection of conflict is the use of an adjustment inventory which the patient can fill out at leisure. Let me state, however, that adjustment inventories help the doctor but not the patient. What helps the patient is the insight he gains with the help of the doctor.

Until now I have talked about the importance of finding out how the patient feels about himself, his problems, and others, as well as the type of doctor one has to be in order to help the patient. Now, I would like to say a few more words about anxiety, the common denominator of a great many emotional disturbances, and its physical equivalents.

The text books define anxiety as "an unpleasant emotion caused by a conflict of opposing forces." This emotion can either be accompanied by certain physiological changes related to the cardio-respiratory and vaso-motor systems (experienced as palpitation, shallow or rapid respiration, sensation of tightness or lump in the throat, trembling, "fluttering" in the abdomen, and sweaty, flushed or pale skin) or be displaced through certain parts of the body (known as organ neurosis or psychosomatic symptoms). In some, anxiety often manifests itself in compulsive, obsessive behavior and phobias.

For the last two years, I have used the questionnaire prepared by Dr. John Mitchell and published in the Tenth Series of *The Letters of The International Correspondence Society of Allergists*. In this, the patient is asked whether, in addition to the presenting symptoms, he either has or has had fainting spells, nightmares, sleeplessness, restlessness, lump in the throat, conscious heartbeat, indigestion, diarrhea or constipation, itching of the rectum or vagina, frequency of urination, sighing respiration—in short, whether he has had physiological equivalents of anxiety or other organ neurosis and, also whether there has been a childhood history of bedwetting, thumb sucking, nail biting, temper tantrums, destructiveness, phobias and fears. If the patient has or has had many of the above-named symptoms, then a diagnosis of psychoneurosis can be made on positive evidence and not by exclusion of organic factors alone or by intuition.

In describing the tissue findings in allergic diseases, the pathologist talks about certain findings being characteristic of allergy but not pathognomonic; the same thing can be said when we study emotions of an allergic patient. There is a great deal of evidence that his symptoms may have meaning and that we can get from them some understanding of what is going on within the individual.

Some of you may say, "Why not refer the allergy patient with a psychosomatic component to a psychiatrist?" There are many reasons for not doing so. The most important one, however, is the fact that the majority of people still think that there is something the matter with their minds or that we think they are "crazy" when they are referred to a psychiatrist. Secondly, since the first interview is the most impor-

tant one, because it is as much treatment as fact-finding, the patient feels terribly let down if, after he opened up to you and told you everything about himself, you send him to someone else. Thirdly, if you can be the type of doctor I have described, you will be able to help many without a psychiatrist. Occasions do arise, however, and frequently, when I do refer patients to psychiatrists, because some patients require deeper psychotherapy and will not respond to simple ventilation, dilution, and the support from someone they feel is interested in them.

In conclusion, let me say that I am still an allergist. My patients are examined for infection; are still given skin tests, blood studies, and x-rays; and do receive hyposensitization treatment. What I tried to bring out in this paper is that my results are much better; and, as an allergist, I am less frustrated since I have been conscious of my patients as personalities with wishes, fears, hopes, and attitudes toward their parents, husbands or wives, brothers, sisters, doctors, and employers, besides being a collection of organs or having a specific sensitivity to certain substances.

I realize that there is nothing new in this approach—the good family physician has always used it. What I have tried to bring out, however, is that, while in the past it was an intuitive gift granted to a few, now many more of us could study and treat the psychological and allergic factors in their mutual inter-relationship if we would make use of the vast amount of knowledge dynamic psychiatry has accumulated.

The books listed in the Bibliography have been very helpful to me.

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REACTION TO PENICILLIN—LEIBOWITZ AND SCHWARTZ

general condition so alarming that death seemed imminent. These symptoms were controlled with oxygen, subcutaneous epinephrine and intravenous aminophylline. Following these episodes, his chronic asthma was not relieved and he was readmitted to the hospital for further study and treatment.

Physical Examination.—Temperature was 100.4° F.; pulse, 124; respiration, 28; and the blood pressure, 148/102. Examination revealed a fifty-eight-year-old man of average height and slender build. His skeleton was medium in size, muscles light and panniculus, thin. There was a loss of elasticity of the skin and generalized poor muscle tonus. He looked older than his stated years and appeared to be chronically ill. The eyes and ears were negative. The nasal mucous membrane was red and edematous and the septum was deviated to the right. The pharynx was moderately injected, and the tonsils absent. The trachea was in the mid-line. The antero-posterior diameter of the chest was greatly increased. This measurement approximated the lateral diameter. Percussion note was hyperresonant. Breath sounds were asthmatic throughout both lung fields. Coarse expiratory râles obliterated all other sounds. Heart sounds were entirely obliterated by the emphysematous chest and the coarse wheezes. Abdomen was flat. Wrinkling of the skin denoted recent loss of weight. Extremities and reflexes were normal.

Laboratory Examinations.—Urine was normal throughout; blood count revealed nothing except for 3 per cent eosinophiles; sputum, no acid-fast bacilli in direct smear; throat culture, streptococcus viridans, pneumococcus, m. flavus and m. catarrhalis in moderate numbers; sedimentation rate, 17 mm. per hour; vital capacity, 2300 c.c.; venous pressure, 90 mm.; circulation time (Decholin-arm to tongue) 18 seconds; electrocardiogram tracings suggested myocardial damage; roentgenogram of chest revealed increased hilar markings.

Clinical Course.—The patient's asthma was considerably improved with repeated injections of epinephrine, aminophylline and oxygen inhalation. The wheezing disappeared in a few days. Intradermal testing with penicillin in a dilution of 1000 units per cc produced an immediate marked local reaction. The maximum diameter of the wheal and area of erythema was 7 x 4 cms. Also, an erythematous papular eruption appeared over the entire medial surface of the arm. Almost immediately, a severe constitutional reaction took place, characterized by dyspnea, cyanosis, wheezing, and cough which was controlled by repeated injections of epinephrine and aminophylline. Passive transfer to the arms of three other patients was negative.

DISCUSSION

Therapeutically, aerosols are used chiefly to enable a drug to reach the depths of the lungs. The clinical effectiveness of the inhalation of penicillin aerosol in bronchial asthma has been described by Barach¹. In aerosols the penicillin mist will penetrate the alveoli where a local concentration will be reached which cannot be obtained by intramuscular injection. With penicillin aerosol therapy the Gram-positive organisms disappear and are replaced by Gram-negative organisms. Favorable reports have appeared in the use of penicillin aerosol therapy, notably by Segal⁴, Barach¹ and Vermilye⁵, with no reactions as described in this paper.

As previously explained, reports of this type of reaction, as presented, are lacking in the literature, except for the one reported above.² It is our

(Continued on Page 689)

REACTION TO PENICILLIN—LEIBOWITZ AND SCHWARTZ

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DISCUSSION

Therapeutically, aerosols are used chiefly to enable a drug to reach the depths of the lungs. The clinical effectiveness of the inhalation of penicillin aerosol in bronchial asthma has been described by Barach¹. In nebulized penicillin mist will penetrate the alveoli where a bacterial reservoir will be reached which cannot be obtained by intramuscular injection. With penicillin aerosol therapy the Gram positive organisms disappear and are replaced by Gram-negative organisms. Kavallaris et al.² suggested that the use of penicillin aerosol therapy, usually by nebulizer, may be an "Aeromycel", with no reactions as described in the paper.

As previously explained, hypoxia of the capillaries of the respiratory tract may be in the bronchi, except for the large vessels of the trachea.

COSMETIC SENSITIZERS

FRANCIS M. WHITACRE, Ph.D., and RITA C. PARSIL, B.A.
New York, New York

RECENT activity on the part of the Federal Food and Drug Administration, the American Medical Association, and other organizations toward more rigid control of the manufacturing procedures and the ingredients used in cosmetic preparations has prompted many manufacturers to scrutinize their products.

Since the use of cosmetics has increased so tremendously in the last ten years (816 million dollars being spent in 1948) the number of cases of dermatitis of cosmetic origin has correspondingly increased. In line with these trends and with the rising public interest in scientific achievement, many more persons who might have given up the use of cosmetics ten years ago are now demanding that we do something about their cases. As a part of a continuing study toward the production of better and especially so-called hypoallergenic cosmetics, the authors have reviewed the literature with special attention to that of the past decade for data which might lead to the formulation of less sensitizing products.

It is the purpose of this paper to list many known sensitizing agents which may be used in several cosmetic items and to list references to the literature. Only the most clear-cut cases have been selected. These are to serve as a guide to collaborating scientists in their initial search for new or altered cosmetic formulations.

The first step toward the solution of the patient's problem is to find out which cosmetic ingredient is the offending agent. Many published case histories show that a certain cosmetic is sensitizing, but the author was either unable to trace the exciting ingredient or had no time to do so. Some papers report that the dyes were responsible for sensitivity but they fail to name the dyes. Other papers may give conflicting data concerning certain ingredients as sensitizing agents of a cosmetic item. Of course, this is common with biological data during the early stages of investigation, but it may be due largely to the fact that the investigator has not been provided with full information regarding the materials with which he has been supplied. It is difficult, therefore, for the busy physician to isolate an individual ingredient from an offending cosmetic in order that he may advise his patient what to do so that she may still enjoy the use of cosmetics.

The manufacturer of cosmetics should be willing and ready to supply test kits and specifications of ingredients to the physician. The principal obstacle to this procedure is secrecy. It is believed by some that they may be protected from competition by preserving secrecy. Today this

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is an erroneous opinion except for the secrecy of the "know-how." Scientifically formulated cosmetics as the result of research toward the production of a desired effect, if something new, can probably be patented. (If it is not new and it is good, it will be copied). Research accompanying the formulation period will probably result in a "know-how" that can also serve as some protection. The discriminatory release of formulas to physicians should, therefore, not be dangerous to the manufacturers.

Assuming that test kits for cosmetic ingredients are available or that the formulas for all cosmetic preparations are available to the physician, still other problems arise in the determination of the contact excitant.

1. Will the single ingredient give the same response as when it is incorporated with other constituents?
2. Does the area on which the test is run react the same as the area on which the cosmetic is used?
3. Was some other cosmetic used in conjunction with the suspected sensitizer?
4. Has the test sample been contaminated?
5. Was the offending cosmetic free from all contaminating agents such as mold, bacteria, machine oil, cleaning solvents, and other foreign matter peculiar to the manufacturing area?

Inasmuch as cosmetic allergy usually manifests itself as contact dermatitis without hereditary influence, with no demonstrated reagins or antibodies in the blood and no accompanying eosinophilia, the mechanism of tissue alteration is still a puzzle. All of the above factors, therefore, must be seriously considered by the collaborating physician and the manufacturer. Single ingredients and combinations of two or more ingredients should be tested. The areas taken for patch testing must be carefully selected by the physician based upon his experience with such tests. The physician must record all cosmetics used by the patient according to his routine in establishing the case history so that incompatible cosmetics may be discovered. On the other hand, the manufacturer must supply carefully packaged test samples free from all extrinsic contamination so that the physician can compile accurate data on the sensitivity of his patient. Finally, the manufacturer must supply a finished product made of the highest grade ingredients and made under rigid rules of cleanliness and careful control checking to insure the absence of molds, bacteria and other possible contaminating agents. This is very important because it is common knowledge that the allergens in contact dermatitis range from simple salts to complex chemical structures, and the number can, therefore, run into the thousands. Occasional contact with low concentrations of these highly sensitizing contaminants may cause violent reactions which could brand an otherwise innocuous cosmetic allergenic.

In the accompanying tables the principal sensitizing ingredients of several of the most widely used cosmetics have been listed together with references to the literature.

COSMETIC SENSITIZERS—WHITACRE AND PARSIL

TABLE I. FACE POWDER

Ingredient	Use	Toxic	Irritant	Sensitizer	Ref.
Aluminum stearate	Adherent	—	—	—	—
Chalk	Absorbent, bloom	—	—	—	—
Kaolin	Absorbent, adherent	—	—	—	—
Magnesium oxide	Opacity	—	—	X	2
Magnesium carbonate	Absorbent, perfume base	—	—	—	—
Magnesium stearate	Adherent	—	—	—	—
Magnesium trisilicate	Absorbent	—	—	—	—
Silica	Adherent, slip	Silicosis	—	—	31, 43
Starch	Absorbent, slip, bloom	—	—	X	44, 50
Talc	Slip	Granuloma	—	—	72
Titanium dioxide	Opacity	—	—	—	—
Tragacanth gum	Binder	—	—	X	11
Zinc oxide	Opacity	—	—	—	—
Zinc stearate	Adherent, slip	—	On inhalation	—	37, 16
Orris root	—	—	—	X	89, 60
Metallic lakes of aniline dyes	Color	—	—	X	26
Oxides of iron ochres	—	—	—	—	—
umbers	Color	—	—	—	—
sienna	—	—	—	—	—

TABLE II. ROUGE

Ingredient	Use
Cake Rouge	—
Rice Starch	—
Talc	See Face powders
Zinc Oxide	—
Zinc Stearate	—
Liquid Rouge	Gel
Methyl cellulose	—
Sodium alginate	Suspending agent
Cream Rouge	—
See cold cream pigments and colors	See lipsticks
perfumes	See chart on perfumes

POWDERS

When made from the ingredients listed in Tables I and II, face powders, rouge, dusting powders and talcums are relatively free from danger to the user. Long continued or concentrated exposure by inhalation to those containing silica and zinc stearate may produce dangerous conditions. Talc when used on broken skin may lead to granuloma. Most sensitizing reactions from powders have been traced to perfumes and to the pigments used for effecting the desired shades. In most cases where the pigment has been thought responsible it has been found that in reality the reaction was due to failure of the manufacturer to remove traces of intermediates which were sensitizers.

Face powders can be beset with danger to hypersensitive individuals if the manufacturing techniques, although relatively simple, are not properly controlled. The greatest care should be exercised in cleanliness of equipment and personnel, the selection and handling of ingredients, and the packaging of the finished product. Traces of cleaning solvents, machine lubricants, mold spores, package liners, and other contaminating materials peculiar to the manufacturer's compounding areas are likely to introduce sensitizing agents into an otherwise safe powder.

CREAMS

Plain cold creams and vanishing creams are usually found to have low incidence of sensitization or irritating effects. In both the principal offender is probably lanolin or cocoa butter. Perfume is also a common offender in cold creams. In vanishing creams a faulty formulation may cause irritation due to the improper balance between the basic and acid ingredients.

Lotions, astringents and tonics may contain sensitizing ingredients, most of which have been referred to above. They may also cause irritation due to dehydration or defatting of the tissues to which they are applied.

TABLE III. LIPSTICK

Ingredient	Use	Irritant	Sensitizer	Reference
Bee's wax	Body binder	—	X	67, 87
Butyl stearate	Dye solvent	—	—	—
Carnauba wax	Body, rigidity	—	—	—
Castor oil	Dye solvent	—	X	92
Ceresin	Stiffening agent	—	—	—
Cetyl alcohol	Dye solvent, emollient	—	—	—
Cocoa butter	Body (low M.P.)	—	X	91
Dimethyl stearate	—	—	—	—
Glycerine	Solvent for plasticizer	—	X	82, 54, 74, 24, 79
Lanolin	Emollient	—	X	82, 54, 74, 24, 79
Lard	Solvent	—	—	—
Orokerite	Body (high M.P.)	—	—	—
Paraffin	Body (high M.P.)	—	—	—
Paraffin liquified	Lubricant, gloss	—	X	52, 7, 56, 39
Petroleum jelly	Lubricant	X	X	17, 52, 7, 56, 39
Spermaceti	Emollient (low M.P.)	—	—	—
Stearyl alcohol	Dye solvent	—	—	—
Vegetable oils	Gloss	—	—	—
Tetrabromofluorescein	Dye	—	X	80, 79, 73, 35, 28
Dibromofluorescein	Dye	—	X	80, 79, 73, 35, 28

LIPSTICK

With lipstick the selection of base materials should be subject to rigid specifications. The same rigid controls should exist in the manufacture and handling of materials as should be observed in the manufacture of all cosmetics. For the most part, however, the indelible dyes used in the lipstick appear to be the principal offending agents. Here again it is suspected that the failure to remove all traces of intermediates is largely responsible for the sensitizing effects of the dyes. Such meticulous purification procedures are costly and may be prohibitively so if carried beyond reasonable limits.

Some manufacturers supply lipstick test kits which are available to the physician and which may be used to advantage in tracing offending ingredients. Some of these manufacturers provide special lipsticks made according to the physician's request and thus allow many women to use lipstick who otherwise cannot tolerate any of those available for purchase. Increasing use of such service will enable newer blends to be made for wider use by hypersensitive persons.

NAIL POLISH

For the most part nail polishes are made from a nitrocellulose base into which certain other synthetic resins, principally the phenol formaldehyde

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TABLE IV. NAIL POLISH

Ingredient	Use	Sensitizer	Reference
Nitrocellulose	Base	X	57, 12, 46, 23, 21, 58
Ester gum	Gloss, adhesion	X	40, 57
Glycol ether	Solvent, plasticizer	X	58, 92
Formaldehyde resins	Gloss, adhesion	X	53, 57, 58, 75, 30, 46, 23
Alcohol	Solvent	—	92
Ethyl acetate	Solvent	X	92
Toluene	Solvent	X	92
Butyl acetate	Solvent	X	92
Amyl acetate	Solvent	X	92
Butyl alcohol	Solvent	—	92
Dibutyl phthalate	Plasticizer	X	92
Ethyl lactate	Plasticizer, solvent	—	92
Rosin	Gloss	—	92
Dammar	Gloss	—	92
Spruce gum	Gloss	—	92
Copal	Gloss	X	92
Ethyl cellulose	Base	—	92
Mastic	Gloss	—	92
Alkyd resins	Gloss	—	—
Castor oil	Plasticizer	X	92
Methyl ethyl ketone	Solvent	X	92, 30
Polyethylene	Bottle closure	—	92
Nylon	Brush stem	—	92
Vinylite	Brush bristle	—	92
Camphor	Bottle closure	X	92
Santolyte M.S.	Plasticizer	X	92

or the sulfonamide formaldehyde types, plasticizers and a combination of solvents have been blended. There are several contradictory reports upon the effect of the nitrocellulose bases. The prevailing opinion at present is that the synthetic resins used in conjunction with the nitrocellulose are the principal offenders. There is considerable evidence, much of it as yet unpublished, that several of the solvents and plasticizers which are commonly used are responsible for so-called nail polish dermatitis.

The bottle closures and applicators, if not properly selected, may also contain sensitizing agents.

In the tables covering some ingredients that have been tried for the possible formulation of a hypoallergenic nail polish, several known sensitizers have been listed. Most of them were in combination with an ethyl cellulose base and were tried on patients with known sensitivity to common nail polishes. This method, however, rules out effects that might otherwise occur when complex mixtures of the otherwise innocuous single ingredients are used. Many more systematic studies must be made before definite conclusions can be drawn as to the effects of combinations.

HAIR PREPARATIONS

Hair dyes, rinses, and restorers are in widespread use. Many dangerous reactions have resulted from the application of these materials.

For the most part hair rinses are relatively safe for home use in that they consist chiefly of vegetable colors. They impart colors by adherence to the hair rather than by actually coloring the hair shaft.

Hair restorers which have been in use for years depend upon the production of a metallic sulfide by combination of the sulfur of the hair with a metallic salt. The principal danger is the toxic reactions that may occur through careless use of the metallic salts.

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Hair tonics and scalp preparations many times contain irritants and
except by experts and then only after careful patch testing be done
individuals and even fatalities have been reported from the use of hair dyes
of new formulation.

Ingredient	Toxic	Irritant	Sensitizer	Reference
Cellosolesives	X	—	—	20, 55
Sulfonated oils	X	—	—	—
Keratin	X	—	—	—
Potassium sulfite	X	—	—	20
Ammonium carbamate	X	—	—	20
Sodium carbamate	X	—	—	20
Keraya gum	X	—	—	68, 59
Acacia	X	—	—	26
Treacle	X	—	—	26
26	—	—	—	26

TABLE VII. HAIR PREPARATIONS, WAVE PREPARATIONS

Ingredient	Toxic	Irritant	Sensitizer	Reference
Caster oil	—	X	—	92
Peru balsam	—	—	—	—
Castor oil	—	—	—	—
Cocoa butter	—	—	—	82, 54, 74, 24
Lanolin	—	—	—	—
Oxyguanidinium sulfate	—	—	—	—
Chitosan hydroxide	—	—	—	—
Eugenol	—	—	—	34, 33, 28
Camphorides	X	—	—	42
Quinine	X	—	—	34, 83, 84, 27
Chlorophyllin	X	—	—	19, 4, 15, 13
Quinone	X	—	—	71, 70
Aspergillus	X	—	—	59, 32
Oxycholosterin	—	—	—	—

TABLE VI. HAIR PREPARATIONS, TONICS

Ingredient	Toxic	Irritant	Sensitizer	Reference
Paraphenylenediamine	X	—	X	93, 90, 26
Paraphenylenediamine dyes	—	—	—	3, 41, 78
DYES	—	—	—	—
Copper salts	—	—	—	90
Bismuth citrate	—	—	—	86, 88, 90
Lead acetate	—	—	—	77
Nickel ammonium sulfate	—	—	—	90
Manganese acetate	—	—	—	86
Nickel chloride acetate	—	—	—	86, 90
Pyrogallol	—	—	—	86, 3
Silver nitrate	—	—	—	—
Manganous acetate	—	—	—	—
Ammonium dyes	—	—	—	—

TABLE V. HAIR PREPARATIONS, DYES AND RINSES

Ingredient	VEGETABLE COLORS	Sensitizer	Reference
Henna	X	—	63, 76
Wattle leaves	X	—	90
Indigo	X	—	15
Chamomile	—	—	—
Sage, salvia	—	—	—
Indigo leaves	—	—	—
Camomile	—	—	—

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COSMETIC SENSITIZERS—WHITACRE AND PARSIL

sensitizing agents. These should be suspected when allergic symptoms develop.

Wave sets, eyebrow and eyelash dyes should be used with caution. Some have been reported to have produced disastrous results.

TABLE VIII. PERFUMES

Ingredient	Irritant	Sensitizer	Reference
Linaloic Oil	—	×	86
Cassia	—	×	86
Lavender	—	×	86, 49
Pinene	—	×	86, 45, 8, 66
Orange	—	×	86
Lemon	—	×	86, 45
Bitter Almond	—	×	86
Orris	—	×	86
Ihlang-Ihlang	—	×	86
Bergamot	×	×	33, 25, 49, 64
Synthetic Jasmine	—	×	9
Methyl Heptine Carbonate	—	×	38, 5, 78
Geraniol	—	×	45
Citral	—	×	45

SUMMARY

In summary, we have presented a list of the most common cosmetic ingredients. Many of these have been reported as being sensitizers by the indicated investigators.

We have pointed out that the greatest care should be exercised in the selection of cosmetic ingredients.

We have emphasized the fact that faulty techniques in manufacturing and packaging may lead to the introduction of allergenic materials which may nullify the care taken in the selection of ingredients.

We recognize the difficulties that exist in the tedious screening that is sometimes necessary to establish the identity of a sensitizing ingredient and offer our facilities in whatever way we can aid the allergist.

We believe that by continuous collaborative effort, no matter how difficult and involved a case of cosmetic allergy may appear to be, there is always hope of finding a cosmetic, whether it be a regular product of a hypoallergenic cosmetic house or a special formula, which will not sensitize the patient. The result will be a satisfied patient, added knowledge to the formulating chemists, and new, beneficial products to sell.

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COSMETIC SENSITIZERS—WHITACRE AND PARSIL

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DISCUSSION

BOEN SWINNY, M.D., San Antonio, Texas: I am sure we all appreciate this authoritative information on the toxic, irritant and sensitizing properties of the various constituents of cosmetics. Also, I am sure we all appreciate the care with which the so-called hypoallergenic cosmetics are prepared. I believe these hypoallergenic manufacturers have done much to clean up the cosmetic industry of this country. For example, one thing we are rarely now seeing is clinical orris root sensitivity.

As scientists, we are interested in whether or not a certain product is a primary irritant or sensitizer, but, practically, we are interested in relieving our patient. If we take a patient off a cosmetic that is producing a dermatitis and she gets well, the result is the same whether it be toxic, irritant or allergic.

I have been rather amazed since the war at the large numbers of patients I am seeing with cosmetic dermatitis caused by the cream-based shampoos and soaps. I should like to ask the essayist what constituent or what property it is of soap and cream-based shampoos that is causing this influx of patients.

Many of the old offenders, such as arsenic, lead, flaxseed and mercury, are being removed from hair tonics and creams, but there still are a few products which contain these. We are still seeing, occasionally, violent dermatitises due, particularly, to the arsenicals and, occasionally, we are seeing asthma or headache due to the flaxseed contained in hair tonics. Also, we are seeing an occasional patient who absorbs enough egg or milk from a shampoo containing these foods to produce symptoms.

SENSITIZERS IN COMMONLY USED COSMETICS

Potassium Arsenite:

Bakers' Hair Tonic
Nixodene

Mercury:

O. K. Beauty Lotion
Stillman's Freckle Cream
Mercolized Wax
Golden Peacock Bleach
Ovelmo

Phenol:

Noxzema

Lead:

Preacher's Hair Tonic

Lanolin:

Wildroot Cream Oil Hair Tonic
Jenis Cream Oil Hair Tonic
Vaseline Hair Tonic

Egg:

Richard Hudnut Egg Shampoo

Milk:

Milky Fluff Shampoo

Flaxseed:

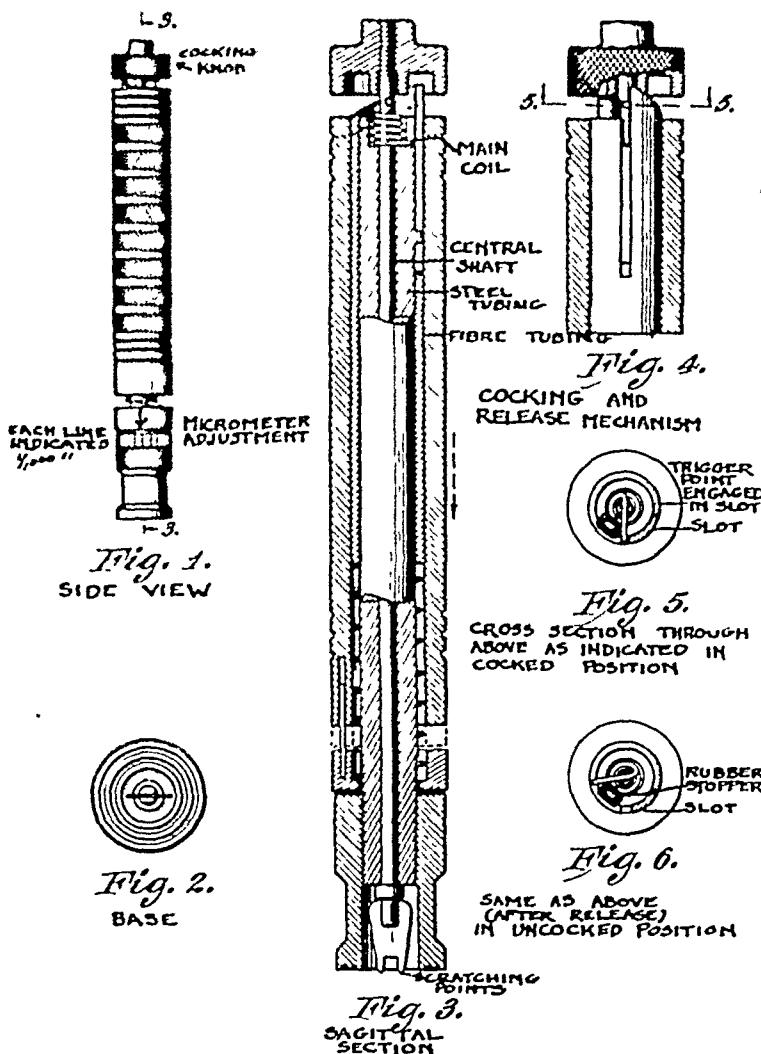
Kremi Hair Tonic

AN INSTRUMENT DEVISED TO PRODUCE PAINLESS SCRATCHES

IRA R. MORRISON, M.D., F.A.C.A.

Atchison, Kansas

THE purpose of this paper is to describe an instrument* which was devised to simplify the task of scratch testing children. Because of the ease with which it produces painless scratches it has also been used on adults scratch tested at the clinic during the past eighteen months.



Figs. 1 through 6. Drawings to show mechanical construction.

DESCRIPTION

The entire instrument, about the size of a stubby fountain pen, is composed of a central steel shaft enclosed in a steel tubing which, in turn, is

From the Allergy Clinic, University of Kansas Hospitals.

*Micrometer-Sratcher is the trade name of the instrument.

encased in an outer fibre tubing (Figs. 1 and 3). A steel base is threaded onto the steel tubing to form a micrometer that may be adjusted to allow the instrument to produce a scratch of any desired depth (Fig. 3). At the top of the central shaft is a knob which, when rotated 270 degrees in a clockwise direction, engages to cock the mainspring (Figs. 3, 4 and 5).



Fig. 7. Photograph showing a scratch being applied and three scratches that have been previously applied at the time indicated.

The bottom of the shaft carries the scratching points made in a single unit of highly tempered nickel-steel (Figs. 2 and 3). When released to rotate, each point moves with great rapidity through an arc of approximately 270 degrees, producing circular scratches 3 millimeters in diameter. A second spring (Figs. 1 and 3) just above the micrometer serves to prevent the release of the trigger mechanism until a skin pressure of approximately 2 pounds is reached. When the trigger mechanism (Fig. 4) is thus automatically released, the central shaft is allowed to whirl rapidly in a counter-clockwise direction. The micrometer is calibrated in units of $1/1000$ inch, allowing for the production of scratches 0 to $25/1000$ inch in depth; the depth of the scratch remains constant for any given setting. Adjustments finer than $1/1000$ inch have been found impractical. Each vertical stripe on the base (Fig. 1) indicates a $1/1000$ inch change in the depth of the scratching blades. Rotating the base to the left increases the depth of the scratch; turning it to the right decreases the depth of the scratch. The base or skin contacting surface (Fig. 2) is ridged so that the area of skin being scratched will be held taut. These furrows also serve to identify the location of the delicate abrasion.

TECHNIQUE

Prior to the application of each scratch the cocking knob must be rotated about 270 degrees in a clockwise direction, or until a loud click is heard and felt, which indicates that the device is cocked and ready for use. The instrument is then grasped by its fibre sheath, as one would hold a dart, and pressed against the skin. When a pressure of approximately 2 pounds against the skin is reached, the mainspring will be automatically released, allowing the central shaft to whirl in a counter-clockwise direction. The depth of the abrasion will depend upon the setting of the micrometer. Once the depth of the scratching points has been set it is usually unnecessary to readjust them unless a very delicate or unusually coarse skin is encountered.

ADVANTAGES

The three chief advantages of the instrument may be listed in decreasing importance as follows:

The scratch is painlessly produced, unless it is too deep. Scratches deep enough to draw blood have at times been accidentally produced over bony prominences, especially in the case of thin individuals.

It produces a scratch of the same length and the same depth whether applied by the expert or the novice, thereby minimizing the human element.

The depth of the scratch may be varied to correspond with the texture of the individual skin.

SUMMARY

The instrument described in this paper is capable of producing painless scratches that are consistently uniform in length and depth. The depth of the scratching points may be regulated to within 1/1000 inch. The device makes possible the application of uniform scratches by the assistant untrained in the art of consistently applying uniform scratches in the conventional manner.

METEOROLOGIC FACTORS

(Continued from Page 644)

unfavorable weather condition observed is dampness, most people are convinced that moisture is the cause of their inhalant allergies.

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425 E. Wisconsin Avenue

AN EVALUATION OF PERAZIL IN ALLERGIC RHINITIS

NORMAN J. EHRLICH, M.S., M.D., F.A.C.A., and MORRIS A. KAPLAN,
M.S., M.D., F.A.C.A.
Chicago, Illinois

After several years' evaluation of various antihistaminic agents it would seem self-evident that except for some differences observed by individual investigators as to percentages of effectiveness and toxic side effects, almost all of us would subscribe to the fact that whereas one drug is effective in one individual, another in a second, and still another in a third, there is basically, from a clinical standpoint, very little else to recommend one drug more than another.

During the hay fever season of 1949, we undertook to evaluate clinically another newer antihistaminic drug,* which purportedly^{1,2} had two outstanding advantages over those previously available—namely, a definite longer duration of effect and minimal side reactions. Following the results observed during that season, it was felt that evaluation in non-seasonal rhinitis might also be of considerable value, and therefore its study was continued for many months beyond the ragweed season.

The patients with seasonal pollenosis, with few exceptions, were all undergoing hyposensitization therapy and were instructed to take the medications only if and when they were experiencing difficulties and, if necessary, to repeat the dose as often as three times daily. Each patient was given a sheet to fill out, indicating the number of tablets taken and the hour of medication, any side effects experienced, and the degree, if any, of relief obtained.

A total of 181 patients were studied, of whom ninety-five had seasonal pollenosis and eighty-six non-seasonal rhinitis. Those with seasonal pollenosis took an average of four tablets a week, and at this time we had a moderately severe ragweed hay fever season. Frankly, we felt that this was a remarkable record, in view of the fact that the next closest drug required a dose 50 per cent greater. A few of these patients were physicians, and invariably their comment was that one tablet seemed to be effective for fully twenty-four hours. Of course, lay patients made no such observations, but the mere fact that so few tablets were ingested would seem to indicate that the benefits were of considerable duration.

In the general evaluation, we separated the seasonal from the non-seasonal cases, since those in the former group could be assumed to have similar exposures to causal allergens.

Table I shows ninety-five patients with ragweed hay fever, of whom forty-one were children under eighteen years of age and fifty-four were adults. Of this total six reported no relief of symptoms whatsoever, fifty reported a fair degree of relief (this we feel is naturally equivocal),

*Perazil—Supplied by Burroughs Wellcome & Co.

PERAZIL IN ALLERGIC RHINITIS—EHRLICH AND KAPLAN

TABLE I. RESULTS WITH PERAZIL IN POLLEN HAY FEVER

Number Patients	DEGREE OF RELIEF				Number Tablets (1 week)	SIDE REACTIONS				
	None	Fair	Good	Excellent		Severe Drowsiness	Nausea	Vomiting	Diarrhea	Headache
Children 41	2	20	7	12	191	6	1		1	1
Adults 51	4	30	8	12	194	10	1	2	1	1
Totals 95	6	50	15	21	385	16	2	2	2	2

TABLE II. RESULTS WITH PERAZIL IN NON-SEASONAL RHINITIS

Number Patients	DEGREE OF RELIEF				Dosage	SIDE REACTIONS				
	None	Fair	Excellent	Dosage		Severe Drowsiness	Severe Headache	Mild Headache	Mild Nausea	Mild Drowsiness
Children 52	7	22	23	50mg B.I.D.					1	2
Adults 34	4	10	20	50mg B.I.D.		3	1	2	1	4
Total 86	11	32	43			3	1	2	2	6

fifteen reported good relief, and twenty-four reported excellent results. The onset of relief varied from thirty minutes in thirty-three patients, to longer than one hour in twenty patients. An average of 385 tablets were taken by these patients in one week's time, making an individual average of four tablets for each patient each week. No patient took more than two tablets in any one day. The side reactions varied from severe drowsiness occurring in sixteen individuals, to mild nausea and headaches in each of two individuals, and vomiting and diarrhea in one. The incidence of side effects was therefore 23 per cent. On the other hand, eighty-six patients with non-seasonal rhinitis were instructed to take two tablets daily, one in the morning on arising and the other at 6:00 p.m. unless side reactions were such as to necessitate discontinuance. Of this total, four had to discontinue the drug because of the severity of the side effects; ten others had mild side effects such as drowsiness, headache, and nausea.

Table II gives the detailed breakdown of these cases. Side effects here were manifested in 16 per cent of the patients.

Combining the two series of figures, we then had 181 patients on this drug, with side effects occurring in nearly 20 per cent of the cases. In evaluating effectiveness we might consider those reporting fair results as equivocal and disregard them, in which case the figures for effectiveness would be approximately 45 per cent. Although nothing outstanding can be noted about the effectiveness or low incidence of side reactions with this drug, we do feel that its longer duration of effect is one to merit consideration; even effectiveness and incidence of toxic side effects compare favorably with other antihistaminics on the market.

(Continued on Page 712)

THE PREVENTION OF INFECTIOUS ASTHMA

A. E. FISHMAN, M.D., F.A.C.A.

Philadelphia, Pennsylvania

IN a survey of the estimated prevalence of specified chronic diseases in the United States, 1937,¹⁷ asthma and hayfever are *fourth* in number of cases, being outnumbered only by rheumatic diseases, heart disease, arteriosclerosis and hypertension. However, if the number of cases of chronic bronchitis and sinusitis are added to the asthma and hayfever group, they then become second, being outnumbered slightly by rheumatic diseases many of which are also due to infectious agents and bacterial allergy.

The prophylaxis of asthma is a most important phase in its management, yet great pessimism is widely prevalent in the practice of its prevention, particularly of the infectious types. This has led to frequent failures and given many a sense of defeat. The elimination of the allergic factor, hyposensitization, general medical measures and good hygiene must be practiced, but in spite of these, infectious asthma is often not prevented. It is well known that many asthmatic seizures are precipitated or are entirely caused by upper respiratory infections. To date, no prophylactic measures outside of the aforementioned plus removal of foci of infection and climatic change have been used in infectious asthma. These measures have been of some benefit to a fair percentage of patients but they have not been of value in many instances. Injections of vaccines in infectious asthma have benefited enough patients so that they continue to be used. However, the results of vaccine therapy are not uniform, the dosage is a most individual problem, and no general conformity is possible. Skin response to vaccines is unreliable, and therapeutic results are unpredictable and often hazardous. Whereas, one individual may be able to withstand an injection of several thousand million organisms with impunity, another may be incapacitated with severe asthma or other general reactions with an injection of several hundred organisms or less.

Being aware of the remarkable results obtained in the prevention of rheumatic fever,^{2,4-6,8,13-16,18-20} and of the greatly reduced incidence of upper respiratory infections particularly of the streptococcal, pneumococcal, and meningococcal groups with sulfonamides,^{1,3,7,9-12} an attempt was made to use these drugs in the prevention of infectious asthma.

Reviewing some of the literature pertinent to the prevention of rheumatic fever and upper respiratory infection, it is striking to note the success obtained in tremendous large scale case reports. Coburn and Moore, Thomas and France, France and Reichsman, Caroline Thomas,¹⁴ Norman

Read at the meeting of the Philadelphia Allergy Society, October 12, 1949.

INFECTIOUS ASTHMA—FISHMAN

Boyer,² Robert Feldt,⁶ Charles Connor,¹ and others, attest to the excellent results with sulfonamide prophylaxis in rheumatic fever. Studies made at the Irvington House Sanitarium showed that only one of a group of fifty-four on sulfonamide prophylaxis developed "strep" pharyngitis, whereas in a control group of fifty-four, thirty cases developed "strep" pharyngitis with subsequent manifestations of rheumatism in fourteen after a latent period of three to twenty-one days. In an Army Air Force Rheumatic Fever Control Program under Col. W. P. Holbrook⁸ there was a 50 per cent to 75 per cent reduction of incidence of respiratory disease and "strep" infection by the use of sulfadiazine prophylaxis. No serious drug reactions were encountered. Coburn,³ of the Navy, in 1944 reported on 39,000 men given sulfadiazine continuously in doses of 0.5 gm. daily from December, 1943 to April, 1944. Hemolytic "strep" infections were prevented in 85 per cent. Constitutional reactions occurred in .01 per cent. C. B. Thomas¹⁵ advocated sulfadiazine 0.5 gm. twice daily for five years or more to prevent recurrences of rheumatic fever. She showed that these children suffered no longer from most bacterial infections although they may develop the common cold in mild form, influenza and virus diseases of childhood. Captain R. G. Hodges⁷ found sulfadiazine very effective, as a prophylactic drug against streptococcal and pneumococcal infections as well as against rheumatic fever and other respiratory diseases. Toxic reaction danger is small as shown by the U. S. Navy program. Mild reactions as transient skin eruptions developed in 0.3 per cent to 0.6 per cent while serious reactions as exfoliative dermatitis and agranulocytosis were exceedingly rare among the five hundred thousand men given sulfonamide prophylaxis for six months. The reports on the preventive effects of sulfonamides in respiratory diseases comprises hundreds of thousands or perhaps over a million cases with rather remarkable effects and with an astounding low incidence of serious reactions. W. H. Oatway, Jr.,⁹ found that after treatment of chronic bronchial infections with sulfonamides that freedom from symptoms remained by giving 0.5 gm. sulfadiazine t.i.d. B. W. Billow and M. S. Albin¹ reported on the efficacy of sulfonamide prophylaxis in the decline of upper respiratory infection, rheumatic fever, lobar pneumonia, atypical pneumonia and absolute prevention in meningitis in twenty thousand soldiers who received one gram daily for five weeks. Two cases of meningitis appeared two weeks after the sulfonamide prophylaxis was discontinued. H. Rusk¹⁰ and M. Siegel^{11,12} have added contributions to the literature on the use of sulfonamides in respiratory tract infections.

With this tremendous clinical background we undertook to study the value of sulfonamides in the prevention of infectious asthma. Although only twenty cases are reported of the patients selected for this study, those chosen were patients who had recurrent or perennial infectious asthma or bronchitis who failed to respond to medical, rhinological, bron-

choscopic or allergic management. Drug and vaccine therapy were of minor value. Climatic change was of no prolonged benefit. Although antibiotics relieved many of these individuals during acute episodes and reduced the seriousness and the course of their infection, the chronicity of the disease often remained for long periods and asthmatic recovery was slow. We felt the prevention of infectious asthma was much to be preferred over the treatment. Generally one gram of equal parts of sulfadiazine and sulfamerazine was given daily in two doses to patients weighing over 100 pounds and under sixty years of age. (Only 0.5 gm. daily was given to those under 100 pounds and over sixty years of age.) Most patients were started October, 1948, a few as early as September, and several in November. The dose was cut to 0.5 gm. daily after April 15, 1949, and continued as such until June 1, 1949. Vaccine therapy plus other allergic and general measures were continued although they had been of apparently minor benefit before. Penicillin was considered as a prophylactic, but since the clinical background of the sulfonamides was so much more extensive in prophylaxis, we decided in their favor especially when we considered that penicillin might be needed for infection that might arise during sulfonamide prophylaxis. As the experiment turned out, penicillin was not needed but in one instance in a patient who discontinued the sulfonamides for over six weeks. However, as evidence is gathered penicillin may well be the drug of choice in future prophylactic experiments.

The patients were given 0.5 gm. of sulfadiazine-sulfamerazine mixture twice daily and instructed to drink one glass of water with each dose. Several patients also took 10 grains of soda bicarbonate with each dose. Only one patient experienced a rash, but she was also sensitive to phenobarbital and iodides which she was taking concurrently. Three patients who stopped the sulfonamides for several weeks experienced a recurrence of their asthma following an acute upper respiratory infection. The others who continued sulfonamide medication continuously had no serious breakdowns even with upper respiratory infections. After several days the upper respiratory disease subsided without manifestations of severe asthma.

The time loss from work or school with this procedure was not longer than three days in any case, whereas in previous years these same individuals were incapacitated with asthma from ten days to six months as an aftermath of acute respiratory infections.

To demonstrate the striking benefits obtained from sulfonamide prophylaxis the following case reports are offered.

Case 1.—L. K., a young girl, aged seventeen, suffered from severe asthmatic seizures and yearly attacks of status asthmaticus for the past ten years, being hospitalized for oxygen therapy at least once every year between the months of October and May. She has been under competent medical and allergic management all this

INFECTIOUS ASTHMA—FISHMAN

time. A sojourn to Florida was of no benefit since she developed status asthmaticus there that required hospitalization. Her general health and physical development were under par as a result of her frequent severe seizures. In addition to allergic management sulfonamide prophylaxis was started October, 1948, and continued daily until June 1949. No severe attacks of asthma occurred although she developed three "colds." Mild wheezing appeared with these colds but were relieved by ephedrine. The "colds" lasted no longer than three days. No time loss from school was necessary throughout the year.

Case 2.—D. R., aged thirty-seven, experienced attacks of asthma for the first time four years ago although he was subject to frequent "colds." He had recurrences of severe asthma every winter. Status asthmaticus occurred in the winter of 1947 to 1948. He was hospitalized and received five million units of penicillin with some relief but was totally incapacitated for over six months. Hyposensitization with dust and vaccine often precipitated an attack of asthma. Although allergic treatment was continued with minute doses of dust and vaccine, his response was poor. He was placed on sulfonamide prophylaxis from September, 1948, to June, 1949. In the interim he has been employed, with no severe seizures of asthma. Several colds that occurred were transient and any asthmatic symptoms that followed were mild. Epinephrine inhalation which had been used several times daily prior to sulfonamide prophylaxis was not used more than three or four times throughout the eight-month period, and then was used more as a precaution in this man's fear of asthmatic recurrence.

Case 3.—M. P., a man, aged seventy-seven, has had chronic asthmatic bronchitis and hay fever for twenty years. His hay fever had been controlled excellently for the past five years. In the past seven years he was incapacitated at least once every winter with an acute respiratory infection that developed into severe asthmatic bronchitis or pneumonitis. Each attack was severe and prolonged, and occasionally was complicated by auricular fibrillation. Although penicillin shortened the course of these attacks, weakness and chronic asthmatic bronchitis remained for months. Sulfonamide prophylaxis was started October, 1948. He went through the entire winter with no attacks of asthmatic bronchitis or pneumonitis even on 0.5 gm. sulfonamide mixture daily.

Case 4.—E. C., a young woman, aged thirty-three, had severe asthmatic seizures of prolonged duration (several months) every fall and winter. Although she improved on allergic management which included dust and vaccine therapy, she had severe attacks of asthma with every upper respiratory infection. Sulfonamides were given and no asthmatic attacks occurred from October, 1948, to February, 1949. For some reason she stopped the sulfonamides and within three weeks an acute asthmatic seizure was precipitated by a "cold." After being brought under control sulfonamides were again given prophylactically and she has been well since.

Case 5.—C. C., a man, aged thirty-one, had severe attacks of asthmatic bronchitis as a yearly winter occurrence for the past four years. In spite of medical management his asthma started earlier and ended later every year. Sulfonamide prophylaxis was initiated in October, 1948. He was well until March when he discontinued the sulfonamides for economic reasons. Within three weeks asthmatic seizures persisting for eighteen days followed a "cold." After this bout he was again placed on sulfonamides with no further asthma.

Case 6.—W. D., a man, aged forty-eight, had yearly recurrent attacks of asthmatic bronchitis or pneumonitis. Although he responded well to penicillin and bronchodi-

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lator drugs, he was often acutely ill and lost several weeks of work every winter. Sulfonamide prophylaxis was instituted in October, 1948. He has had no severe seizures and has lost no time from work this year.

These few case reports demonstrate the effectiveness of sulfonamide prophylaxis in infectious asthma particularly in those uncontrolled by other measures. We are well aware that many cases of infectious asthma are controlled by other procedures, but in those not controlled this has been a most effective prophylactic measure. We are not advocating mass sulfonamide prophylaxis for respiratory infections or where allergic, medical or other therapy has been effective. But we definitely feel that sulfonamide prophylaxis (or other antibiotic prophylactic measures that may be warranted in the future) is of value in those cases of recurrent infectious asthma or bronchitis that are not prevented by allergic or other types of management. Allergic and medical measures however must be continued and with the addition of sulfonamides previous failures are converted into success with gratifying results to the patient and the doctor.

SUMMARY

1. Twenty patients with regularly recurrent infectious asthma and/or bronchitis who failed to respond to allergic or other treatment were given sulfonamide prophylaxis for periods of seven to nine months.
2. No severe attacks of asthma or bronchitis occurred in any who took the prophylactic treatment faithfully.
3. No general reactions occurred. One case of skin eruption appeared in a patient who was sensitive to other drugs.
4. This method of prophylaxis is recommended for the prevention of infectious asthma in those patients who have recurrent attacks of asthma caused by respiratory infections for which other methods of treatment have failed.
5. Allergic and medical management should be continued along with sulfonamide prophylaxis.

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255 South 17th Street
6610 Woodlawn Avenue

AN UNUSUAL ALLERGIC REACTION TO PENICILLIN

(Continued from Page 669)

belief that these reactions occur more frequently than the search of the literature indicates. These reactions are manifestations of sensitivity to penicillin itself and not to impurities in the penicillin solvent. Penicillin has an amino-acid like structure and can act as an allergen just as any other allergen. It is possible that penicillin itself may also act as a hapten in combination with body proteins as a sensitizing agent. It was demonstrated by Chow and McKee, that there could be a combination of penicillin and serum albumen producing a penicillin-protein combination complex.

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511 Avenue P (Dr Leibowitz)

ALLERGY TO CASTOR BEAN DUST WITH REPORT OF A CASE

MAURICE KAUFMANN, M.D.

Lexington, Kentucky

THE explosive suddenness with which a susceptible individual may react to castor bean dust and the severity of the resulting symptoms places this substance in a position of importance as an allergen. The allergic consequences, particularly if the causal agent is not recognized or if proper treatment is not instituted, make it a very dangerous allergen in those industries and occupations in which exposure to it is unavoidable.

According to Feinberg⁵ (1946) the most important product of the castor bean is castor oil, which is used for medicinal purposes, chiefly as a cathartic. However, castor oil is also widely used as a lubricant; in the manufacture of artificial leather; for leather dressing; as a varnish ingredient; in the preparation of perfumed oils, hair dressing, lipstick, and other cosmetics; as an ingredient of rotogravure ink and other dyes; and for the manufacture of plastics. Castor bean meal, the residue remaining after extraction of the oil, is in considerable demand.

According to Ratner and Gruchl⁸ (1929), the manufacturing process consists of extracting the oil from the castor bean by compression, which leaves a residue or cake. This cake is then ground or pulverized to form, what in the trade is known as, castor bean "pomace." This pomace, because of its high nitrogen content, makes it a very desirable fertilizer. Commercially, it is sacked and sold for this purpose.

From a chemical study, Osborne, Mendel and Harris⁷ (1907) concluded that the castor bean contains proteins of the same character as other oil seeds, namely, a considerable quantity of crystallizable globulin, proteoses, and a smaller amount of coagulable albumin. They ascribed the toxic action of the castor bean to the protein fraction, which is an albumin coagulable at 60 to 70 degrees.

Stillmark¹⁰ (1888) showed that the castor bean fraction without the oil has the property of hemolyzing and agglutinating the red blood cells, *in vitro*, of nearly all warm-blooded animals. He gave it the name "ricin." This substance has since been proven to be a toxalbumin and to rank among the most powerful of vegetable poisons.

Bernton³ (1923) commented that the toxic action of the castor bean is well known and that the ingestion of the whole bean, accidental or otherwise, or even the ingestion of castor oil for medicinal purposes, on occasions, has had dire results.

Sollmann⁹ (1936), in his discussion of ricin, states:

"This toxin is contained in the castor seeds but does not pass into the oil. The ricin is responsible for the toxic effects on eating the castor seeds; five or six of these are fatal to a child; twenty to adults; three or four seeds may cause violent gastro-enteritis with nausea, headache, persistent vomiting, colic, sometimes bloody

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diarrhea, thirst, emaciation and great debility. The symptoms usually do not set in until after several days. More severe intoxications cause small frequent pulse, cold sweat, icterus and convulsions. Death occurs in six to eight days from the convulsions or from exhaustion. The fatality is about 6 per cent. This small fatality is due to the destruction of the poison in the alimentary canal. The treatment would be evacuant and symptomatic. Three to ten days are required for complete recovery."

Sollmann states that a preparation of ricin has been obtained which is a typical albumin and which is so active that 0.0005 mg./kg. is fatal to rabbits. The fatal dose to man would therefore be about 0.035 mg. or 1/2000 grain. This was first shown to be so by Osborne, et al⁷ (1907). Sollmann also states that ricin has a very powerful agglutinating action, *in vitro*. Leukocytes, epithelial and other cells are agglutinated. The presence of serum hinders the agglutination.

It is well known, of course, that Ehrlich⁴ (1891) did some of his basic work with ricin. He found that injections of this phytotoxin produces an antitoxin (antiricin), and that an animal so treated can survive the injection of 5000 ordinary fatal doses of ricin. Immunity starts in five to six days and lasts for six or seven months. The antiricin is contained in the pseudoglobulin fraction of the serum and contains antitoxin, antiagglutinin and precipitin.

The castor bean meal is fraught with danger for man and beast. When used as a fertilizer, either alone or combined with fodder, it may poison cattle. Exposure to its dust may result in irritation of the conjunctival, nasal, oral, pharyngeal, laryngeal and bronchial mucous membranes. The skin may also be affected. Therefore, those who come in contact with the castor bean or its dust—those engaged in the manufacture of castor oil, or in the packing and shipping of the meal, or as farmers or gardeners—should be warned of its potential dangers.

Bernton³ (1923) reported a case of castor bean allergy in a research chemist who, in the course of his duties, had been exposed to castor bean. His allergic manifestations included asthma and rhinitis. There had never been any personal or family history of allergy. This patient was subjected to a complete and thorough investigation. Not only was he tested qualitatively but also quantitatively. When he was tested for the degree of his sensitivity to castor bean meal, a cutaneous reaction was obtained with a drop of a 1:250,000 dilution of the protein solution of the meal.

Figley and Elrod⁶ (1928) investigated an "asthma colony" in Toledo, Ohio, and found that the condition was due to castor bean dust emanating from a neighboring castor oil factory. The incidence of asthma in the "colony" was in direct proportion to the amount of exposure to castor bean dust but not to the personal and familial allergy history prior to the exposure. They described the castor bean dust as being relatively odorless when compared, for example, to the fumes of linseed oil or flaxseed.

On microscopic examination, they found the particles of the castor bean dust to be the same size as ragweed pollen. The weight of the dust was exactly the same as that of a given amount of pure giant ragweed pollen. This, of course, would explain the ease with which wind carries this dust.

Figley and Elrod did not attempt any desensitization in their series of cases but when they tested two persons, who had given delayed reactions to scratch tests, intradermally using 0.01 cc of 1:1000 extract of castor bean dust they obtained severe inflammatory reactions with widespread aseptic lymphangitis of the entire arm which prostrated these two patients for several days. Subsequently, however, these patients did not suffer with asthma for a period of several weeks even though they lived close to the castor oil mill and had had almost continuous asthma before. Their neighbors who were asthmatic from the same cause and who were not "treated" continued to have symptoms. The authors point out that the asthma in their cases was a specific allergic reaction to the castor bean dust, rather than a toxic one due to irritation and prolonged contact.

Ratner and Gruehl⁸ (1929) reproduced the specific clinical picture of anaphylaxis in the guinea pig with the same materials which brought it about in human beings. They showed that the toxic element, ricin, could be clearly differentiated from the allergic element.

Barnard¹ (1930), in a report of seven patients who were sensitive to castor bean extract, stated that he was able to remove the ricin present in the extract without altering its activity.

Bennett and Schwartz² (1934) reported two cases of acquired castor bean dust sensitivity which was characterized by sneezing, coryza, itching eyes, cough and wheezing respiration. One patient also developed urticaria of the face, neck and hands. The authors stress that caution must be observed in testing with castor bean dust extract. They state that although other potent extracts such as horse dander, horse serum, rabbit epithelium, cottonseed, pollen and fish are tested with high dilutions, castor bean extract requires still higher dilutions for testing in order to avoid constitutional reactions.

CASE REPORT

The following case presents additional evidence that castor bean meal or dust is a most potent allergenic substance and should continue to be regarded as such.

On July 20, 1949, M.C.N., an adult, male Negro, was referred for allergic consultation. His occupation at that time was that of truck driver and general helper for a landscape and gardening firm. His present illness began on July 14, 1949 when at about 3:30 p.m., while spreading and distributing some fertilizer (which subsequently proved to consist of castor bean meal) on a lawn in the performance of his work, the wind suddenly shifted and blew the meal into his face and body. Fifteen to twenty minutes later his eyes began to smart, itch and tear. His nose felt itchy, and he sneezed in barrages. The exposed skin of his face, neck, ears, and

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arms began to burn and itch. He stated that by the time he arrived at the doctor's office his throat had become swollen and sore and his nose so stuffy that he could hardly breathe and he felt as if he was choking. He had developed welts all over his exposed skin where the meal had come in contact with it.

The referring physician stated that when first seen by him, the patient had a severe urticarial eruption on his face, neck, and arms, was in rather severe distress with dyspnea, coughing and wheezing, and complained of choking with a tightness in his mouth, nose and throat. His eyelids were edematous and his conjunctivae were injected, swollen and chemotic. His lips were puffy, and the mucous membranes of his oropharynx were edematous throughout.

Emergency treatment was given in the form of epinephrine injections, antihistaminic drugs by mouth, and calcium gluconate intravenously. He soon experienced some relief of his general symptoms and was referred to an ophthalmologist who prescribed Antistine (R) and butyn eye drops and wet, boric acid compresses. He continued to use the local eye medication and to take the antihistaminic drugs by mouth. His symptoms began to abate, but four days later, he was re-exposed to the meal in trying to obtain a sample for investigative purposes. He insisted that the material be placed in a paper bag by someone else and that he carry it at arm's length. Nevertheless, all of the foregoing symptoms recurred, and he again required epinephrine injections for relief.

When the patient was seen two days after his second exposure, he was not in extreme distress but did appear to be ill. Detailed questioning elicited no personal or family history of allergy. Physical examination revealed a well-developed, male Negro, twenty-nine years of age, 72 inches tall and weighing 178 pounds. His oral temperature was 99.4 degrees, pulse 76 and blood pressure 126/84. His face was swollen and the skin on his cheeks, eyelids, lips, ears and neck was somewhat edematous. There was no urticaria. The conjunctivae and scleras of both eyes were markedly congested. There was lacrimation and photophobia. The nasal mucous membranes and turbinates were red and edematous. The faucial inlet, including the uvula, as well as the posterior pharyngeal wall, was inflamed. The airway, in general, seemed adequate. Pulmonary findings, including fluoroscopy, were not significant. Cervical adenopathy was present. The remainder of the physical examination revealed no pertinent information.

On July 21, 1949, he was patch-tested on the flexor surface of the right forearm with dry castor bean meal and with castor bean meal moistened with normal saline. The patient was warned that if any burning or itching took place underneath the patches he was to remove them immediately, notifying the physician. The burning and itching occurred in about twelve hours, and the patient removed the patches but, unfortunately, because it was about 2 a.m., the patient, out of consideration, failed to call at that time. When he reported about twelve hours after he had removed the patches, he stated that upon removing them he noted a welt about the size of a quarter at the site of the dampened meal. By careful questioning, it was concluded that at this site he must have had a wheal about $2\frac{1}{2}$ cm. in diameter with pseudopodia, surrounded by erythema. At the site where the dry meal had been placed there could still be seen a papular eruption with several of the papules coalesced into one raised area, roughly 1 cm. at the greatest diameter, surrounded by a faint rim of erythema. The patient remarked that at the time he had returned for the sample of fertilizer some of it must have fallen on his arm because he had a few little "spots" which looked exactly like the papules which were present under the dry meal. Even though over seventy-two hours had passed, I could see, upon close examination, residual papules at the locations which he pointed out to me. These, as well as those at the area of the dry meal application, persisted in burning and itching even after three days, particularly when he perspired.

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On July 23, 1949, using 1/20 normal sodium hydroxide as a control and as a diluent, scratch tests were performed to castor bean meal dust; pollens of ragweed, grass and plantain; inhalants, including dust, cat epithelium, dog epithelium, horse dander, horse serum, chicken feathers, goat epithelium, pyrethrum, orris root, glue, wool, cottonseed, flaxseed, kapok, silk and tobacco. Within fifteen minutes after the scratch test to the castor bean meal dust, a wheal 1.5 cm. in diameter with pseudopodia and erythema developed and persisted for more than an hour. Since negative results were obtained with all the allergens except castor bean meal dust, intradermal tests were done with the same allergens, excluding castor bean meal dust. The results of the intradermal tests, except the one with the dust concentrate extract, were negative. With the dust extract, a wheal about 1 cm. in diameter with very little pseudopodia and practically no erythema occurred.

The patient continued to improve very slowly and was advised to take the antihistaminic drugs, bronchodilators, if necessary, and strictly to avoid any contact with castor bean products.

SUMMARY

A case of castor bean meal dust allergy has been presented, together with a review of the literature. The serious results from contact with this allergen have been stressed. Those whose occupation may expose them to this material, should be warned as to its dangers. Caution must be observed by allergists in testing for sensitivity to this potent allergen.

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MOLDS AS INHALANT ALLERGENS

CLIFFORD H. KALB, M.D.

Milwaukee, Wisconsin

OUR interest in allergenic molds is reflected in a long chain of observations up the years from miasmatic effluvia to our present position where a tremendous literature on the mycologic aspects of antibiotic research affords us a sounder, more comprehensive background from which to expand our appreciation of the clinical problems presented by the mold allergies.

It will be recalled that prior to Van Leeuwen's observations^{14,15,16} on the environmental aspects of mold spore exposure, little of a specific nature had been published to guide us in our interpretation of these mold spore responses. Through his efforts, Hansen,¹¹ Jiminez-Diaz and others^{12,13} were stimulated to investigate allergic responses to a relatively small group of mold spores commonly encountered within the home.

This emphasis on the environmental pattern of mold spore exposure by the European School found its counterpart in a broader point of view as pioneered by Stakman,^{25,26,29} Durham,^{2,3,4,5} Bernstein and Feinberg,^{1,6,7,8,9} Prince, Morrow et al,^{17,18,19,20,21,22,23,24} Wittich^{26,27,28,29} and Hansel.¹⁰

No doubt, emphasis in this country on the general nature of mold spore problems was influenced by our initial concentration on the widespread respiratory problems presented by atmospheric pollinosis, its logical parallel. Whatever may have been the logic or the need, the published data relating to spore-incidence curves across the country and throughout the seasons now enables us to evaluate seasonal sensitivity to the spores of Fungi imperfecti almost as clearly as we do those stemming from a specific response to the pollens of locally encountered trees, grasses and weeds.

Having provided ourselves with a workable program for handling the atmospheric type of mold problem, it appears fitting and proper to renew our interest by more fully evaluating those frequently overlooked environmental sources for mold spore development and circulation within the home itself. Before presenting a few clinical experiences encountered in evaluating inhalant mold patterns within the home, let us first look at an example of the usual atmospheric mold type of problem as we see it in the midwest.

A. K., a sixty-one-year-old woman, has annually had an incapacitating degree of seasonal asthma since childhood. Dissatisfied with attempts at ragweed hyposensitization elsewhere, she has, for some years, been spending the fall in California, where she has been more or less free of distress. The fact that symptoms in Wisconsin preceded actual ragweed pollination and persisted far beyond the pollination period of this particular allergenic weed raised the suspicion of atmospheric mold spores as possible offenders. Positive delayed skin tests to and properly graduated hyposensitizing doses of Fungi imperfecti enabled this patient to remain in Wisconsin with very

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Doctor Kalb is an Associate Fellow of The American College of Allergists.

minimal symptoms throughout the fall following six months of allergic management. This is the sort of person for whom windy days in the autumn and open bedroom windows at dawn are anathema.

An interesting observation among children has been the occurrence of severe episodes of bronchial asthma following raking up and romping about in leaves during October when mold-spore counts in this locality reach a peak. We have encountered a number of mold-sensitive children in whom this suggestive lead was confirmed by skin testing and clinical improvement resulting from hyposensitization to mold spores of *Fungi imperfecti*.

There appear to be, however, more subtle aspects of the problem—features of an environmental nature, of significance in those patients failing to experience perennial relief with so simple an analysis as the foregoing. Attempts to analyze the environmental allergenic pattern frequently bring one face to face with some interesting features relating to the inadvertent cultivation and circulation of allergenic spores within the home.

R. T., the seven-year-old son of a returning veteran, developed bronchial asthma within a few days after his father removed household furnishings from six years of wartime storage and resettled the family in its present home. Since the asthma was almost exclusively related to the child's sleeping habits, the bedroom was held under suspicion. The usual items such as feather pillows, dust-retainers and the rest which generally make up the offending allergenic moiety were ruled out by skin test and trial but when the boy's mattress, from which we obtained *Aspergillus ochraceus* in pure culture, was enclosed in an allergen-proof mattress cover he quickly began to improve.

Incidentally, a deliberate study of several hundred cotton mattresses discloses that, from more than one-third, one is able to obtain a pure culture of *Rhizopus nigricans*.* A later report on reagins by the Prausnitz-Kustner technique to these as well as other specific mold spore responses will be presented.

C. H., a forty-five-year-old woman, was seen for a perennial nasal allergy, unsuccessfully treated by an assortment of nasal medications. Prompt withdrawal of all nose drops left the nose blocked and without the evanescent relief afforded by their decongestive action. In our allergic studies, we cultured *Rhizopus nigricans* from her mattress, whereupon, against advice, she discarded it and purchased a new one from a local department store. This, in turn, yielded a pure culture of *Mucor* sp., so finally an allergen-proof mattress cover was procured and relief obtained. Hypo-sensitization to combined molds and dust has enabled her to remain asymptomatic for months.

C. K., a forty-three-year-old asthmatic patient, as well as I. K., his twenty-one-year-old son (a nasal allergic), experienced increased symptoms after establishing a "beer depot," on the second floor of which he now maintains his residence. A mold-survey (4/9/48) on Sabouraud petri plates revealed a heavy and diversified growth

*Subsequent cultures from bales of cotton as received by a local mattress manufacturer show *Rhizopus nigricans* when samples were taken from the center of the bales. Could this mold be regionally responsible for allergic symptoms in the South where this material originates?

of molds. This patient was hyposensitized to mold spores and his entire establishment fumigated with formaldehyde vapor. In keeping with modern refrigeration procedure, we suggested that he install sterilizing tubular lamps in the area. This was done, and both individuals have, aside from an occasional mild inconvenience, been much more comfortable than heretofore. A subsequently exposed petri plate (7/14/48) revealed a very marked diminution in circulating spores.

M. S., a thirty-three-year-old mother, and her three allergic daughters, ranging from three to ten years of age, had been having severe naso-bronchial symptoms. When first seen, their discomfort, at first seasonal, finally had become perennial, so environmental studies were carried out. Their home, heated by a hot-air type unit, was liberally furnished with mold spores emanating from a damp basement, which contained among other things a mold-laden incinerator. When this was removed, the home fumigated, sterilizing tubular lamps installed, and hyposensitization to mold spores carried out, a very satisfying improvement was noted in all. Within the past month the mother, going into the attic for the annual spring cleaning, was seized with a severe attack of the original symptoms. Investigation revealed a leaky roof with a resulting permeation of the attic contents by molds over-running the mildewed area.

V. K., a thirty-year-old woman, was referred by her otorhinolaryngologist consultant because of repeated polyp formation. When mold spores were found to feature prominently in her allergic pattern, we discovered a major hazard in her husband's enthusiastic hobby of raising rare tropical fish. It appears that the fertility of these fish is dependent upon a diet which includes special grubs raised in moldy bread and soil. Large pans of this mildewed material in the basement provided a constant source of spores, which were actively circulating throughout the house by way of the hot-air heating unit. The husband, with rare good humor and understanding, abandoned his cherished hobby and fumigated the home. His wife's progress from this point on, with proper hyposensitization to mold spores, has well rewarded his sacrifice.

These and similar experiences with musty kapok-filled toys, a baby wrapped in a mildewed blanket during a snow storm, a boy's enthusiastic salvaging of an older brother's mildewed jacket and parka, long ignored on a pile of castaways in the basement, and the exaggerated allergic symptoms accompanying wash day in the basement—these and many others emphasize how mold-supporting peculiarities of the patient's own environment may influence his allergic responses and remind us of the need for environmental mold surveys in an effort to eliminate, as well as to hyposensitize, to molds as inhalant allergens.

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ALLERGY TO VIRAL AND RICKETTSIAL VACCINES Review of the Literature

SAMUEL UNTRACHT, M.D., and BRET RATNER, M.D.
New York, New York

THE propagation of chicken sarcoma on chorioallantoic membrane of the chick embryo¹⁰ led Goodpasture and his co-workers to develop this medium for the culture of fowl-pox and vaccinia viruses.^{2,14} Soon the technique proved successful for the growth of other viruses, among them, the virus of herpes simplex,¹⁵ Newcastle disease⁷ and western equine encephalomyelitis. The latter proved useful in the preparation of a vaccine in sufficient quantity to be applied to the immunization of domestic animals and of man.² Reports on rickettsiae successfully grown on the chorioallantoic membrane appeared in 1934.^{14,55} Bengtson and Dyer³ worked with Rocky Mountain spotted fever in 1935, but it remained for Cox¹¹ to develop a method which made available rickettsial vaccines for large scale production, which soon found application in the armed services. Another technique utilizing the entire chick embryo was presented in the preparation of yellow fever virus vaccines.⁵⁰ Allantoic fluid culture of influenza virus was developed by Burnet⁶ in 1941. In this way, it has become possible to provide a ready source of viruses and rickettsiae for clinical trial. Thus far, the vaccines which may be considered of value as immunizing agents are those against yellow fever, typhus fever, Rocky Mountain spotted fever (tick typhus), Influenza Virus A and B infections, and mumps. There is no doubt that the search for and development of vaccines against other viral and rickettsial diseases will continue. The fact that these disease-producing agents display a great avidity for growing on embryonal tissues of the fertilized egg has brought into sharp relief the possibility of allergic reactivity that must inevitably ensue with so potent an antigen as egg protein.

ALLERGIC REACTIVITY OF CHICK EMBRYO VACCINES IN ANIMALS

The early use of equine encephalomyelitis vaccine (E.E.V.) in domestic animals made it evident that allergic reactivity could result. Schoening⁴⁴ reported local and systemic reactions in horses when reinjected with E.E.V. Anaphylactic shock in some instances terminated fatally. Similar observations were made by Graham.²⁴ Wolfe and Trum⁵³ described anaphylactic shock followed by typical desensitization in the recovery period. Putting these observations to the test of the laboratory animal, van der Scheer et al⁶¹ showed that guinea pigs can be sensitized with E.E.V. and fatally shocked on receiving a second inoculation. Berge and Hargett⁴ ascribed the reactions following E.E.V. to antigens which developed in the older embryo, and which were more active than those of the younger embryo. As a result of guinea pig anaphylaxis experiments, they concluded that typhus vaccine, Rocky Mountain spotted fever vaccine and American "Q" fever vaccine derived from yolk sac of embryos less than ten days of age should prove even less antigenic. Subsequent reports have not supported these contentions as will be shown in the review of clinical experiences which indicate that cultures from younger embryos are highly antigenic. Some indication of the nature of the antigens contained in these vaccines is offered by Cohen,⁹ Knight,^{27,28} Coulson and Stevens,¹⁰ and Engel and Randall.¹⁸

From the Department of Pediatrics, Allergy Division, and Department of Immunology, New York Medical College.

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The predilection of rickettsiae and viruses for specific embryo structures influences the type of egg antigen dominant in the vaccine. The rickettsiae of typhus and "Q" fever thrive best in yolk sac fluid and membrane; of Rocky Mountain spotted fever in yolk sac and chorioallantoic membranes; the virus of influenza, in the amniotic and allantoic fluid, while equine encephalomyelitis and yellow fever viruses thrive best on embryonal tissue, itself. The allergic reactions which ensue may result from such antigenic specificities. An individual predominantly sensitive to egg white might conceivably react to influenza vaccines, as has been emphasized by Ratner and Untracht,³⁶ and one predominantly sensitive to egg yolk would react more markedly to typhus vaccine and less to yellow fever vaccine as has been demonstrated by Rubin.⁴² Another individual, presumably sensitive to egg white and egg yolk, reacted successively to typhus and to influenza vaccine, given a year apart.⁴¹ Experimental support for this capacity for specific reaction is offered by Coulson and Stevens who found that, although egg yolk and egg white have antigens common to both, they also have antigens independent of each other. Some studies indicate that chick embryo and embryonic fluids are more highly antigenic and that vaccines grown on membrane have a reduced anaphylactogenicity. Coulson and Stevens indicated that suspensions of washed rickettsial bodies derived from yolk sac culture contain egg antigens in quantities which are close to the minimum sensitizing dose, while Cox¹² failed to induce sensitivity with Rocky Mountain spotted fever and typhus vaccines derived from membrane inoculated cultures.

ALLERGIC REACTIVITY OF CHICK EMBRYO VACCINES IN THE HUMAN

The experiences with animal immunization have been closely borne out in the use of these vaccines in human beings who have displayed the whole gamut of allergic reactivity.

In the nonsensitive individual, the earliest form of allergic manifestation, namely, a serum sickness-like reaction was described by Sulzberger and Asher⁴³ from primary yellow fever vaccine injection. Symptoms were pain in the joints, headache, fever, nausea and vomiting, with a rash of the urticarial and erythema multiforme types. These appeared six and seven days after the injection, respectively, in two individuals. In a third, the symptoms were similar in appearance, but were manifested earlier, following thirty-six hours after the injection, thus indicating a shortened incubation period.

Local serum sickness-like urticarial rash and induration at the site of injection were noted by Stull⁴⁴ in a thirty-three-year-old man, seven days after injection of 1 cc of E.E.V. That this vaccine may potentiate hypersensitivity was indicated when on reinjection of the same dose two weeks later, a large local reaction appeared within one hour and lasted for six days. A similar episode was described by Lieder²⁹ on second injection of equine encephalomyelitis vaccine. Beard, Finkelstein and Beard,¹ too, have noted more severe effects at the site of reinjected E.E.V. In nine persons who were revaccinated, they observed symptoms of "crampy stiffness" and muscular soreness at the injected area. It is not entirely clear that these reactions are allergic since the dose given was large, and its absorption slow, in view of its heavy protein content, as pointed out by Coulson and Stevens. However, that the vaccine may sensitize and shock horses and guinea pigs has been indicated above.^{4,21,44,51,53} Similar acceleration in the appearance of the local reaction at the site of injection was described by Beveridge and Burnet⁵ after repeated intradermal injection of influenza virus vaccine.

For the most part, the reactions reported occurred in individuals who were spontaneously sensitive to egg proteins. Severe anaphylactic shock reactions have followed injections of yellow fever, typhus and influenza virus vaccines in egg-sensitive persons. In 1943, Swartz⁴⁰ recorded the case of a profound anaphylactic reaction with blurred vision, labored breathing, nausea, vomiting, diarrhea, urticaria,

edema and unconsciousness following a single injection of yellow fever vaccine with cholera vaccine within five minutes after its administration. Skin reactions to egg and chicken proteins were demonstrated as were circulating allergic antibodies. Sprague and Barnard⁴⁶ described similar alarming reactions from yellow fever and typhus inoculations. With typhus vaccine, there have been eight instances of such severe anaphylactic reactions; two additional instances resulted from influenza virus vaccine. Park³¹ reported a reaction to the egg allergen in typhus vaccine. A British airman, aged thirty-five, was admitted in collapse, vomiting blood and presenting asthmatic breathing and generalized urticaria. He soon became comatose. With symptomatic treatment, he recovered completely by the next morning when he related that he had received an injection of typhus vaccine fifteen minutes before the described reaction occurred. He revealed that he had been allergic to egg all his life. His usual reaction to egg was vomiting or, if it did not occur, edema of the lips, tongue and larynx. Asthma and urticaria would follow. Never before had he vomited blood or passed into coma. Skin tests were positive to egg proteins by the scratch method and also with passive transfer tests. Park reported that his patient had received an inoculation of yellow fever vaccine about a year previously without any ill effects. Apparently he was sensitive to the yolk allergen.

Another typical case is that reported by Roth³⁰ in a soldier, aged nineteen. Immediately after the first injection of typhus, the patient had extreme dyspnea, cough, weakness and substernal pressure. He had a temperature of 97.4°F., a pulse rate of 128, and a weak respiratory rate of 24. His skin was cyanotic and covered with an urticarial eruption; his face was edematous; his lungs were filled with asthmatic rales. The patient recovered in four days. Three days later, he was given 0.1 cc of typhus vaccine, and a severe asthmatic attack followed immediately; but he did not have shock or cyanosis as before. He presented asthmatic rales, a temperature of 98.6°F., a pulse rate of 120, and a respiratory rate of 36. Recovery ensued in thirty-six hours. It is of interest that when he was profoundly affected, his respiratory rate was only 24, and later when his reaction was milder, his respiratory rate was 36. This is an important criterion for the severity of an attack; the slower the respiratory rate, the greater the danger of asphyxial death.

Other reports of severe systemic reactions with shock, asthma, urticaria, nausea and vomiting in some instances, have been recorded by Sprague and Barnard,⁴⁶ Hampton,³² Lieder,³³ Plotz³⁵ and Rubin.⁴¹ In the case reported by Plotz, the patient suffered a severe reaction from the test dose when she was tested intracutaneously with typhus vaccine following her recovery from the shock reaction. Further vaccination procedure was therefore withheld. Rubin's case had a recurrence of severe shock one year following the typhus injection when he received 1 cc of influenza vaccine. Within five minutes he developed asthma and generalized urticaria, which gradually subsided in four days. An interesting anaphylactic reaction was reported in a twenty-five-year-old member of the Women's Army Corps.³⁶ She developed a markedly lowered blood pressure about thirteen hours after an injection of 1 cc of influenza vaccine. There was no wheezing or urticaria, the cardinal symptom being a fall in systemic blood pressure. It is probable that this woman suffered a canine type of anaphylactic reaction. She revealed a history of life-long egg intolerance.

Evidence for the dependence of these reactions upon chick embryo and egg sensitivity was obtained from a history of pre-existing intolerance for foods containing these proteins in almost every instance. Swartz, Park and Hampton succeeded in proving the antigenic identity of typhus vaccine with egg proteins by means of skin tests and passive transfers.

Moderately severe systemic allergic reactions have also been described following the administration of typhus, yellow fever and influenza virus vaccines. In these instances, urticaria, angioneurotic edema, gastrointestinal disturbances, milder

asthmatic episodes without shock symptoms were the syndromes which followed prophylactic or diagnostic inoculation. Roth³³ mentions eight moderate allergic reactions after typhus injection, in addition to the severely shocked individual described above. In only four of this total of nine cases was a history of egg sensitivity known to the individuals concerned. Raynolds³⁷ described the case of a nurse who developed a blotchy rash of the face, neck and back fifteen minutes after an intradermal test dose of typhus vaccine. Interestingly enough, there was a negligible dermal response to this test injection. The patient revealed a history of having suffered urticarial rash of the face and neck after eating egg.

Rubin⁴² described a soldier, aged nineteen, who developed edema of the eyes, urticaria of the cheeks and nose, and pain in the chest after an injection of typhus plus yellow fever vaccines. Skin tests on this individual are particularly interesting, since the dominant sensitivity appeared following egg yolk injection, while those to egg white and chicken meat were negligible. Direct test with yellow fever vaccine was two plus positive, while typhus vaccine was four plus. Passive transfer to egg yolk developed a three plus reaction. This individual could tolerate hard-boiled egg white, but vomited when whole egg was eaten. His sensitivity, apparently, depended greatly upon the yolk antigen, and bears out the contention of Coulson and Stevens that egg yolk and egg white may have antigenicity independent of each other.

Three reports are recorded concerning influenza virus vaccine reactions of a moderately severe nature. Eaton and Meiklejohn¹⁵ described one case of moderately severe asthma in an individual who had had no history of allergy previously, and two cases of urticaria. Magill, Plummer, Smillie and Sugg³⁰ mention an instance of angioneurotic edema of the face and lips. Ratner and Untracht³⁶ reported the occurrence of asthma when a nine-year-old boy was tested with influenza vaccine. Another child, aged six years, developed generalized urticaria and asthma after injection of 0.5 cc. In both these instances, there was a history of intolerance for egg or egg-containing food.

The systemic allergic reactions described above are all instances in which the individuals recovered. The hazard of injection of these vaccines into exquisitely sensitive individuals revealed itself in six instances which proved fatal. Three fatalities followed typhus vaccine, one after a spotted fever vaccine, and two after influenza virus vaccine.

Rifkin³⁸ described the case of a soldier, aged twenty-four years, who died twenty-five minutes after injection of 1 cc of typhus vaccine. Autopsy in this case revealed a typical guinea pig type of anaphylactic lung. This individual had a history of nausea on ingestion of egg. Walker⁶² described a sailor who was found dead in his bunk twenty-six minutes after having received his first injection of typhus vaccine. Within five minutes after injection he had complained of feeling ill, but had failed to seek aid. This individual had been obliged on occasion to seek relief from duty because of feeling ill after ingestion of egg. He had been sensitive to egg all his life. It is of interest that he had previously received an injection of yellow fever vaccine with no ill effect. It is not known whether this yellow fever vaccine was of the type cultured on egg embryo media. Autopsy of this case revealed a typical guinea pig anaphylactic lung with multiple hemorrhages.

Plotz³⁵ reported the death of a soldier who had received typhus and cholera vaccines thirty minutes previously. In this instance, too, autopsy revealed typical guinea pig anaphylactic lungs. In the same report, Plotz described the death of a soldier two hours after injection of influenza virus vaccine. This individual had had a history of asthma since childhood. An additional death in this report was that of a child who had received a spotted fever vaccine. The death in this instance was reputed to be typical of anaphylaxis. This case is quoted from the Department

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of Health record in Washington, D. C., and may be the same as the case referred to by Forman.²⁰

More recently, Curphey¹³ reported a case of a three-and-a-half-year-old child who received a subcutaneous injection of 0.5 cc of influenza A and B vaccine. The family physician at the same time administered a similar amount of vaccine to two other sisters, five and eight years, respectively, and also to the mother and grandmother, who received 1 cc each. All the injected individuals had little or no reaction, except the three-and-a-half-year-old, who complained of pains in the abdomen, chills, followed by vomiting and convulsions which developed four hours after the injection of the vaccine. At this time, examination of the child showed a rectal temperature of 109°F.

History revealed no evidence of allergy. On admission to the hospital within two hours after the onset of symptoms, the patient was cyanotic with widely dilated pupils. Moist rales were heard in both pulmonary fields; the heart rate was 180 per minute. The extremities showed convulsive contractions during examinations. Epinephrin and oxygen did not relieve the symptoms. The bleeding time was prolonged, and, moreover, bleeding points appeared wherever a needle was inserted. The temperature fell to 103°F. The heart rate increased in rapidity up to 240 per minute, but remained regular. Cheyne-Stokes respirations ensued. Convulsions occurred every two minutes. Two hours after entry into the hospital, breathing ceased, and after artificial respirations were instituted, the rhythm resumed, but with constant bilateral twitchings and spasms. Seven hours after the onset of symptoms, the child collapsed completely; her condition deteriorated until she died in coma.

Necropsy findings in this case were not characteristic of anaphylaxis—neither the pulmonary type seen in the guinea pig nor the canine type affecting the liver. Curphey regarded it as a hemorrhagic form of anaphylaxis. He considered the hemorrhages as having resulted from a Shwartzman-phenomenon-like reaction. He noted that, on autopsy, an early pneumonia was evident which possibly was due to a virus infection. He reasoned, therefore, that this virus had sensitized the child to such a degree that the prophylactic injection of influenza virus vaccine precipitated a necrotic type of remote response similar to that seen in the Shwartzman reaction in the rabbit. From the fact that this child was not shown to be sensitive to egg and did not show typical anaphylaxis and had a temperature of 109°, which is not consonant with the picture of anaphylaxis, it must be assumed that the child died as a result of the injection, but not necessarily from anaphylaxis.

Salk⁴³ raises the interesting question, as does Curphey, that perhaps the virus, itself, was responsible for the death.

If Curphey's case was a toxic reaction to some "foreign protein," as he suggested in his comment, then the question raised by Salk is of considerable importance. Salk believes that the primary toxic reactions to the virus vaccines are proportional in frequency and severity to the concentration of virus injected. The more severe reactions that were observed in adults, given rather large doses of virus concentrated and purified by differential centrifugation, frequently began four to five hours after injection, a time of onset similar to that in the case described by Curphey. The symptoms and signs of reaction were chills, fever up to 103°F. recorded orally, severe headaches, vomiting, agitation and anxiety, body aches, and varying degrees of prostration. In a few cases, in these experimental studies with large doses, the reactions were somewhat alarming. In a limited experience with young infants and children, Salk found reactions of greater severity, accompanied by higher temperatures than with adults.

To sum up, then, we are confronted with differentiating the true allergic reactions from the nonallergic, or "primary toxic" reactions. The former are: (1) sudden and explosive, (2) with no hyperpyrexia, (3) manifested as dermal, respiratory and anaphylactic shock reactions and, (4) occur in individuals in whom a history of

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egg allergy or the presence of positive skin reactions to the allergen can be elicited. The latter are: (1) delayed in onset, (2) with varying degrees of hyperpyrexia, (3) presenting none of the manifestations of classical allergic reactions and, (4) occur in individuals who do not have a history of allergy to egg or positive allergic skin reactions.

When a patient dies in shock, several of the criteria of anaphylaxis must be present at necropsy, in order to diagnose the condition as allergic. A careful evaluation of the tenets of an allergic, as differentiated from a nonallergic individual, must be made in the final analysis of a case.

The history of allergy to egg is very valuable in appraising hypersensitivity, but is not always so reliable a criterion as one would expect. Swartz,²⁹ for example, in his case obtained the interesting data that, at four years of age, his patient of twenty-seven had been fed large quantities of egg and egg-white during an illness. From that time on, he was unable to eat eggs. He not only had an aversion to them, but the ingestion of the smallest amount of egg-containing food precipitated severe asthmatic paroxysms. He also was hypersensitive to other foods, as well as to feathers. On the other hand, Roth,³⁰ who reported on nine cases of allergic reactions to typhus vaccine obtained a history of allergy to egg in only four. Further, we studied 108 allergic children³¹ of whom only eleven were found sensitive to egg; in two of these, an allergic systemic reaction ensued from the injection of influenza vaccine. Of these two cases, one gave a history of sensitivity to egg from infancy, and the other was not cognizant of his egg sensitivity until it was determined by us three years previously. It was evident from our eleven cases, too, that despite a real history of egg sensitivity the majority did not suffer systemic reactions. Only 50 per cent of them were sufficiently sensitive to egg white to be regarded sensitive to a degree high enough to warrant fear in administering the vaccine.

The striking fact gleaned from our study was that of 108 truly allergic children who were all carefully studied and under observation for one to several years, allergy *per se* was not the dominant factor. Sensitivities other than to egg did not influence the reaction to influenza vaccine at all. Moreover, only two out of the 108 children, or approximately 2 per cent, were truly markedly sensitive to egg white. Therefore, whereas in our paper we regarded 4.6 per cent who had definite marked dermal reaction to egg white as comprising the potential hazards, we now believe that this figure should be reduced to less than 2 per cent. In our paper, we stated, "If the incidence of allergy in the general population is 10 per cent, then the serious egg allergenicity in the general population would be 5 per cent of 10 per cent, or 0.5 per cent, or one in every 200 persons." Corrected as indicated, therefore, the figure should be less than 2 per cent of 10 per cent, that is one, or perhaps two in every 1,000 persons.

If sensitivity to egg is more prevalent among children, as are all food sensitivities, then this figure can be considerably reduced for the general population. If comparable figures are obtained with adults, the exact number for the general population should be small indeed. This is in accord with the point of view of Plotz, and is borne out by the experience in the army, quoted from Hampton.³² A total of 8,419 military personnel were injected at one post between August, 1944 and August, 1945 with typhus vaccine, and only one anaphylactic reaction occurred in this group.

If one in 8,000 or 9,000 adults reacted severely to 1 cc of typhus, then with further purification of the vaccines and small intracutaneous doses of 0.1 cc, the dangers of anaphylactic shock or death will be reduced to the extremely low figure of one in many thousands.

Still another interesting phase of this problem remains for the future—and that is the danger inherent in developing an acquired sensitivity to egg proteins from repeated injections of this type of vaccine.

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The late Dr. Plotz made a real attempt to study this phase.²⁵ Of a group of 150 individuals who were not sensitive to egg and who were vaccinated with three weekly subcutaneous 1 cc injections of typhus vaccine, nine of the 150 vaccinated subjects developed cutaneous sensitivity. In all nine cases, cutaneous sensitivity was noted four weeks after the third dose; one to egg yolk and egg white; four to vaccine, alone; two to vaccine and egg yolk, and two to vaccine, egg yolk and egg white. The cutaneous sensitivity became negative after twelve weeks in seven of the cases, and diminished considerably in two. In these two persons, the cutaneous reactions remained relatively unchanged twelve weeks after the third dose. These two subjects must have been sensitized to a greater degree than the others—they reacted to egg yolk, egg white, and vaccine. Despite the cutaneous sensitivity, all the subjects sustained a subsequent subcutaneous injection of the full dose of typhus vaccine without systemic reaction.

In a study of about 322 children, which is to be published, we noted that no marked cutaneous sensitivity to egg resulted from influenza A and B vaccine administered in 0.1 cc intradermal doses. Similar results are reported by Gold and Hampill with repeated equine encephalomyelitis vaccine injections.²¹

On the other hand, we must conjure with the case of Stull¹⁴ who relates that in a patient, aged thirty-three, a delayed allergic urticarial local reaction occurred seven days after the first injection of 1 cc of equine encephalomyelitis vaccine (local serum sickness-type reaction). Two weeks later, a second injection of 1 cc produced a large local reaction within one hour (accelerated reaction indicating allergy) which lasted for six days. Since that time, this patient has had gastrointestinal disturbances with severe diarrhea following the eating of chicken or eggs. The serum of this recipient contained antibodies to egg yolk and chicken embryo, but not to egg white.

It would be interesting to know how long such clinical allergy persists. In the light of this case, one must recognize that despite the paucity of such occurrences, children and adults may become systemically sensitized to egg protein if the vaccines are used extensively. Here, too, in the reduction of this hazard, much will depend upon the smallness of the dosage and the refinement of vaccines. It must further be remembered that the equine encephalomyelitis vaccine used in this case is about twenty times more antigenic than other vaccines of this group.

Another interesting phase of allergy to virus vaccines cultured from egg embryo is the cutaneous reactivity of a delayed or tuberculin type which follows intradermal injection and results from sensitivity to the virus protein. This dermal sensitivity acquired from natural infection with the viruses and also from prophylactic vaccination is therefore reputed to be useful in indicating the immunologic status of the individual. A negative reaction to a test dose would thus be indicative of susceptibility to infection, whereas a positive response, indicating previous experience with the virus, would point to a state of immunity. With regard to mumps, usefulness of this type of dermal test is at present undergoing clinical evaluation.^{8,16,17,19,20,32} Antigen for the Frei test for lymphogranuloma venereum may be derived from egg embryo culture.²³ Other virus infections which may induce delayed allergic reactivity to virus protein include influenza,⁵ herpes simplex³³ and meningopneumonitis in rabbits.³¹

In conclusion, we should like to state that, whether the individual is highly allergic to egg yolk or egg white the hazard can be minimized if the suggestion made by Ratner and Untracht³⁰ is followed. All persons should be tested intradermally with undiluted vaccine, using 0.02 cc, before administering each and every prophylactic dose to establish whether a person is negative to the egg protein, moderately sensitive, or markedly so. The vaccine should be withheld if the reaction is a systemic or a severe local one. All the studies point to this single criterion as being of value.

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more potent preseasional injections. Of the sixty-five ragweed-sensitive patients receiving this technique, fifty-nine had an excellent result; five good; and one fair.

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482 Beacon Street

Joseph R. Wiseman, M.D., F.A.C.A., and Richard D. Wiseman, M.D., announce their association in the practice of allergy and internal medicine. The address is Physicians Building, 608 East Genesee Street, Syracuse, New York.

Sol N. Keen, M.D., Associate Fellow of the College, announces the removal of his offices from 619 East Fifth Street to 311 East Seventeenth Street, New York 3, New York. Doctor Keen specializes in the practice of pediatrics and pediatric allergy.

IN MEMORIAM

WILLIAM F. PETERSEN, M.D., F.A.C.A. (Hon.)



Members of the College will grieve to learn of the sudden death of Dr. William F. Petersen. On August 7, while at work in his garden in Lake Geneva, Wisconsin, he was suddenly stricken with a cerebral hemorrhage; he was taken to Lakeland Hospital in Elkhorn, Wisconsin, and on August 14 was transferred to St. Luke's Hospital, Chicago, where he died August 20.

Doctor Petersen was born in Chicago, March 25, 1887, the son of Eduard Petersen, founder of the Petersen Oven Company. He attended the Armour Institute, and graduated from the University of Chicago in 1910 and from Rush Medical College in 1912. After doing graduate work in biochemistry and pathology at Harvard and Columbia Universities, he became Instructor and Assistant Professor of Experimental Medicine and Pathology at Vanderbilt University (1913-1917).

During World War I he served in the Army

Medical Corps. In 1919 he married Alma C. Schmidt, daughter of Dr. Otto L. Schmidt of Chicago, physician and historian. They had three sons.

In 1919 Doctor Petersen joined the faculty of the University of Illinois College of Medicine. As Professor of Pathology from 1924 to 1942 he carried on extensive research, publishing—in addition to many articles in medical journals—*Protein Therapy and Nonspecific Reactions*, 1922, and with Dr. S. A. Levinson, *Skin Reactions, Blood Chemistry and Physical Status of Normal Men and Clinical Patients*, 1930. At about this time he became interested in the effect of weather and climate on disease and on the normal population. He was one of the first to investigate this field and to it devoted most of his remaining years. He published his findings in *The Patient and the Weather* (five monographs with M. E. Milliken), 1934-1938; *Lincoln-Douglas, The Weather as Destiny*, 1943; *Hippocratic Wisdom*, 1945; and *Man-Weather-Sun*, 1947. He also found time for activity in numerous medical organizations, serving as president of the Chicago Pathological and Internal Medical Societies, and as chairman of the board of the Institute of Medicine of Chicago. In addition he was active in the management of the Petersen Oven Company of Franklin Park, Illinois, as president and later as chairman of the board.

After retiring from the University in 1942, he devoted much time to community health problems, serving on the advisory committee of the Chicago Board of Health, and helping to initiate the Chicago and Cook County Health Survey of the U. S. Public Health Service. He became interested in the problems of chronic disease, tuberculosis, alcoholism, nutrition, and conservation, serving on various committees and organizations in those fields, among them the Central Service for the Chronically Ill, the Committee for the Study of Cycles, and Provident Hospital Association. He was also Director of Clinical Research at St. Luke's Hospital for several years.

Doctor Petersen was an Honorary Fellow of The American College of Allergists. Other organizations of which he was a member are American Association for the

(Continued on Page 712)

News Items

SOUTHWEST ALLERGY FORUM

San Antonio, Texas, will be the meeting place for the 1951 Forum of the Southwest Allergy Forum, April 8, 9, and 10. Scientific sessions are to be held at the Plaza Hotel. The lighter side of the Forum will include a cocktail party Sunday evening, a cocktail supper and "Night in Old Mexico" at La Villita on Monday evening, and a luncheon for the ladies Monday. Allergists who are interested in presenting a paper at the Forum are urged to send the title immediately to the Secretary-Treasurer, Boen Swinny, M.D. Ideas and suggestions are also welcome.

AMERICAN ACADEMY OF PEDIATRICS—ALLERGY SECTION

At the next meeting of the American Academy of Pediatrics, Allergy Section, in Chicago, seminars on "Eczematoid Dermatoses" will be conducted on October 14 and 15 by Dr. Jerome Glaser, assisted by Dr. Norman Clein. Another seminar, on "Allergy from a Pediatric Viewpoint," will be given by Dr. James C. Overall, who will be assisted by Dr. George Logan of the Mayo Clinic.

There will be two evening panel discussions under the auspices of the Allergy Section. On October 14 at 8:00 P.M. the panel discussion will be on Eczema. Dr. Lewis Webb Hill will be the Moderator, and the panel members will be Drs. Joseph Harman Fries, Arthur J. Horesh, Samuel J. Levin, and Bret Ratner. The Moderator for the panel discussion on Respiratory Allergy October 15 at 8:00 P.M. will be Dr. Bret Ratner, and the panel members will be Drs. William P. Buffum, Susan C. Dees, Lewis Webb Hill, and Edward Scott O'Keefe.

There will also be a luncheon on October 16 sponsored by the Section on Allergy. Informal discussions will be made by Drs. Bret Ratner and Lewis Webb Hill.

PRICE REDUCTION ON CORTONE

Merck & Co., Inc., manufacturing chemists, have announced increased factory production and a reduction of almost 50 per cent in the price of Cortone, the Merck brand of Cortisone. Effective August 21, the price of Cortone to hospitals was reduced from \$95 to \$50 per gram. This is the fifth in a series of reductions which have, in one year, brought down the price to one quarter of the initial investigational price of \$200 per gram.

Good supplies of Cortone are available to more than 6,500 hospitals which have facilities that meet certain minimum requirements. For the present the drug is to be used, during the initial period of treatment, only in patients treated in these institutions. After initial treatment the physician may provide continued treatment in his office or in the patient's home.

Dr. Herbert J. Rinkel, Kansas City, Missouri, a member of the Board of Regents of the College, presented a talk by invitation of Professor Robert Debre, Professor of the Medical Clinic for Children, before the Polyclinic of the Hospital for Sick Children in Paris on the morning of June 30 on "The Problems of Allergy in Pediatrics." Doctor Rinkel's talk was accompanied by colored slides.

BOOK REVIEWS

1949 YEAR BOOK OF DERMATOLOGY AND SYPHILOLOGY. Edited by Marion B. Sulzberger, M.D., and Rudolph L. Baer, M.D., Department of Dermatology and Syphilology, Post-Graduate Medical School, New York University-Bellevue Medical Center. 514 pages, 76 figures. Price \$5.00. Chicago: The Year Book Publishers, 1949.

As these annual Year Books appear, they are convincing evidence of the rapid progress of our knowledge of the subject from year to year. The therapy of certain dermatoses shares the varied uses of ACTH, Cortisone (Substance E), Substance F, and other steroids derived from the adrenal gland. Considerable progress has been made in the penicillin treatment of syphilis. The demonstration of circulating specific antitreponemal antibodies is epochal. Aureomycin and chloromycetin® have proved valuable in treating obstinate dermatologic diseases such as folliculitis and sycosis, Kaposi's Varicelliform Eruption, and some forms of ulcerative stomatitis. Many forms of tuberculosis of the skin are being satisfactorily treated by streptomycin, alone or with Vitamin D₂ and/or para-aminosalicylic acid. Lawrence's studies have demonstrated regularly successful passive transfer of tuberculin-type 24-48 type sensitivity. These findings are of tremendous significance, when including 24-48 hour type sensitivity to bacterial and fungus allergens, and immunologic phenomena of contact-type eczematous sensitivities.

Other important achievements are too numerous to mention here. The review of acne vulgaris and its management is complete. The allergic phase of the dermatoses is adequately presented.

The vast content makes it an outstanding daily reference. The authors' immense experience is reflected by the skill with which all topics receive their proper evaluation.

THE DIAGNOSIS OF SALMONELLA TYPES. F. Kauffmann, M.D., State Serum Institute Copenhagen, Denmark. 86 pages. Price \$2.25. Springfield, Ill.: Charles C Thomas, 1950 (American Lecture Series, No. 62).

A summary of available information on the members of the genus *Salmonella* is given, which will be very useful for those who have already gained experience in the handling of the manifold problems of *Salmonella* identification. The meat of this compilation is the tabulations, which include a listing of types according to groups (196 types are recorded); an alphabetical list of types with references to the first descriptions of the more recently described types; tables on the strains to be employed for the preparation and absorption of immune sera for typing; also on cultural behavior as far as important for type identification.

CLINICAL ALLERGY. By Louis Tuft, M.D., Assistant Professor of Medicine, Temple University School of Medicine and Chief of Clinic of Allergy and Applied Immunology, Temple University Hospital, Philadelphia. Second Edition, 690 pages, 54 figures. Price \$12.00. Philadelphia: Lea & Febiger, 1949.

This timely revision of an excellent clinical first edition is very welcome. With more than a decade elapsing between the two, the accumulated new clinical and experimental data as a result of antihistamine therapy, more extensive studies of the relationship of mold fungi to allergies, aerosol therapy for respiratory allergies, the allergic basis of periarthritis nodosa, the recent experimental observations of Rich indicating that rheumatic fever may be due to an allergy, the observations of others that arthritis is allergic in nature,

the increasing importance of nervous and psychic influences, conclusive proof of atopic allergies in animals simplifying the matter of classification of allergies, and endocrine influences, all indicate the rapid development of our knowledge of syndromes due to hypersensitivity.

However, as in the first edition, clinical procedures based upon sound observations of the author are stressed in detail.

It is replete with details compactly worded so that the new edition is invaluable as a text for the student and practicing allergist. The illustrations are excellent, the blocking of case reports is unique, and the paper stock and binding are of first quality.

PROCEEDINGS OF THE FIRST CLINICAL ACTH CONFERENCE.

Edited by John R. Mote, M.D., with 52 contributors. 607 pages, numerous figures. Price \$5.50. Philadelphia: The Blakiston Company, 1950.

This volume constitutes the Proceedings of the First ACTH Conference held in Chicago on October 21 and 22, 1949, under the auspices of Armour and Company. The events which led to calling the Conference are enumerated. It was finally agreed to call the Conference on behalf of all the investigators to permit exchange of information of these various investigators, who kept their studies on a broad base to ascertain the range of diseases that may be caused by endocrine defects.

Fifty-two papers are presented, together with a summary. They cover such a wide range of observations on various clinical syndromes that they cannot be enumerated here. They range from observations of ACTH on normal individuals of various ages, through its metabolic effects, its relation to other endocrines, its influence on hypertension, kidney diseases, leukemias, malignancies, rheumatoid arthritis, pulmonary infections, and the relief of allergic diseases, to its function in patients with severe personality disorders.

Of particular interest to the allergist would be the papers on "Eosinophil Observations in ACTH Therapy" by Drs. Theron G. Randolph and John P. Rollins; "The Effect of ACTH on the Clinical Syndrome of Dermatomyositis" by Dr. Charles Ragan; "Effects of ACTH in Patients with Collagen and Allied Disorders" by Dr. J. R. Elkinton and associates; "The Effect of ACTH on One Case of Periarteritis Nodosa" by Dr. Ralph Goldman and associates; "Preliminary Report on the Use of ACTH in the Hypersensitive State" by Dr. John E. Bordley and associates; "Relief of Allergic Diseases by ACTH Therapy" by Drs. Randolph and Rollins; and "Studies on the Effect of ACTH on Eosinophilia and Bronchial Asthma" by Dr. Bram Rose. It is now generally recognized that something fundamental in human physiology has been encountered, when adrenal cortical stimulation altered the clinical state of patients in widely divergent syndromes.

The editor realized that the Conference only represents the status report of the projects in progress at the time and that the results presented are not to be considered as final or conclusive. He states, "It is obvious that a tremendous amount of work will be required not only to arrive at valid conclusions concerning the effect of adrenal cortical stimulation in various disease syndromes, but, more important, to elucidate the physiologic and metabolic abnormalities which may be concerned in these various disease states."

It has been practically a year since this Conference was held, and the accumulated experience of hundreds of physicians on hospital staffs who have had ACTH available and have treated hospital patients would indicate that ACTH should soon be made available to reputable physicians who are on accredited hospital staffs, to try in their private practice. Our present stock

BOOK REVIEWS

of information about the treatment of certain distressing syndromes with remarkable relief by the use of ACTH is rapidly taking the drug out of the experimental stage. Laboratory and clinical observations have determined quite accurately the initial and maintenance dosage of ACTH, so that any physician completely familiar with these schedules should be able to safely administer them in his private practice. He should, however, familiarize himself with any untoward reactions, avoid overdosage, and bear in mind that if a patient is carefully watched for any untoward symptoms, unfavorable reactions are reversible.

PERAZIL IN ALLERGIC RHINITIS

(Continued from Page 683)

SUMMARY

Perazil is another antihistaminic drug that compares more or less favorably with others available in so far as effectiveness and side effects are concerned; however, this drug appeared to us to have one outstanding quality to recommend its use; namely, longer duration of effect.

ACKNOWLEDGMENT

This study was made with technical assistance of Ellen Bachenheimer, M. T.

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116 South Michigan Ave.
Suite 909 (Chicago 3)

IN MEMORIAM

(Continued from Page 708)

Advancement of Science, American Association of Pathologists and Bacteriologists, American Society for Experimental Pathology, American Association for Physical Anthropology, American Medical Association, Illinois Medical Society, Chicago Medical Society, Chicago Medical History and German Medical Societies, American Academy of Applied Nutrition, Friends of the Land, Refugee Physicians Placement Committee, University Club of Chicago, Chicago Literary Club, and Chicago Historical Society (governing life member).

His survivors are his widow, residing at 1322 Astor Street, Chicago 10; and three sons: Edward, a resident physician at the University of Chicago; Conrad, in engineering and management with the Petersen Oven Company; and William, attending the Harvard Law School.

The officers and other members of the College extend their sincere sympathies to the family. Doctor Petersen's death is a great loss to the College because of his active participation and interest in its development and because of his pre-eminent prestige.

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THE ELECTROPHORESIS OF EGG WHITE AND CRYSTALLINE EGG ALBUMIN

SAMUEL GROSBERG, M.D.
and
M. MURRAY PESHKIN, M.D., F.A.C.A.

New York City

ANY method by which allergenic molecules are introduced into the skin without breaking the skin would be of service in a study connected with basic skin physiology. Such a technique might also be of service in placing upon a more quantitative basis the method of skin testing in the allergies. A clue to a method of this type was given when it was shown by Abramson and his co-workers that the active molecules of pollen extracts may be electrophoretically transported into the human skin.^{2,3,5} Abramson⁴ has further shown that the main route by which these water-soluble molecules were transported was through the sweat glands rather than through the hair follicles. This was a new method of studying skin reactions by allergenic materials provided that the molecules could be transported by the forces engendered by the electric field. The electrophoretic skin test, therefore, is a technique whereby the allergenic material is introduced not into one site but over many sites with a minimum of skin injury. These observations were confirmed by Morse⁶ with pollen and by Dutton⁷ with pollen and a few other allergens.

In view of the fact that it seemed desirable to study the complex mixture of egg white in detail, and because a child, skin-sensitive by the scratch test and clinically allergic to egg, was available, it was decided to make a quantitative study of the way in which these egg white preparations may be transported electrophoretically into the human skin. In this way data pertinent not only to skin permeability to these molecules which are different from pollen might be obtained, but in addition fundamental observations on the patient's reactivity to egg white molecules introduced into the skin to form skin deposits would be observed.

METHOD

A galvanic circuit with single electrodes, canton flannel pads, and aluminum contacts previously described, was employed.⁵ A special electrophoretic apparatus to be described was also tested.⁴ A current density of not more than 0.5 ma per cm² employing both poles, was used. Because of the extreme clinical and skin sensitivity of the patient, small areas only were tested, the maximum area being 4 cm², with the time three minutes. Suitable control experiments were simultaneously made.

A stock solution of egg white was made up without saline. This was done to prevent the salt solution from carrying the current rather than the allergenic molecules themselves, and to preserve electro-osmotic flow within the skin near its maximum. The stock solution of egg white was diluted with glycerin so that in general the dilutions were made from a 50 per cent solution of glycerinated egg white. Since egg white contains approximately 17 per cent protein or protein-like material, the stock solution contained 8 per cent of egg protein. Crystalline egg albumin was chemically prepared in the usual manner.

SUBJECT

The experiments were done on N. R., a white boy, four and one-half years old, first seen on October 7, 1947, when he weighed 35 pounds and was 41 inches tall. At the age of three months a rash appeared on both thighs. The rash spread to other parts of the skin and was aggravated each year during the summer months except for 1947, when the skin cleared from June to mid-September.

At four years of age the oral administration of aspirin caused urticaria. On September 7, 1947, whole milk was accidentally spilled on his chest and soon hives appeared over the areas of the skin in contact with the milk.

Sneezing and leaking from the nose lasting for several hours after arising in the morning commenced at the age of two and one-half years. These perennial nasal symptoms were aggravated during the summer months. At the age of about three years, during the winter, he experienced the first attack of asthma. Subsequent attacks occurred at intervals of one or more weeks with each attack lasting several days. Some of these attacks of asthma were accompanied by a fever and were initiated by infection of the upper part of the respiratory tract. Ingestion of egg also caused asthma.

There were no important childhood diseases. A paternal aunt had eczema.

Physical examination was essentially negative except for a grayish pallor of the mucous membranes of the middle turbinates and dry, elevated, red patches on the skin involving the left wrist, penis, thighs, and the lower abdominal area.

Sensitization skin tests (scratch and intradermal techniques) revealed

positive reactions to egg white, lactalbumin, mustard, pork, radish, white potato, spinach, grass pollen, plantain, and chicken.

Diagnosis: Neurodermatitis (chronic eczema), contact urticaria (milk), drug urticaria (aspirin) and allergic rhinitis (perennial and seasonal).

The boy was placed on a restricted diet, which removed eggs in any form and permitted the use of evaporated cow's milk, along with anti-allergic environmental contact restrictions. External medication was employed for the eczematous skin lesions. After the fourth day, the skin lesions showed progressive improvement until the skin cleared except for one small patch of dry eczema on the dorsal aspect of the left wrist which remained in the following year of 1948, when the electrophoretic experiments with the egg white antigens were begun.

EXPERIMENTS

The experiments were done at intervals of one week. The anterior aspect of the forearms was used in all experiments. The 50 per cent egg white-glycerin mixture (approximately 8 per cent protein) was diluted with water, with a control of a similar dilution with 50 per cent glycerin.

April 27, 1948: With the solution of $1:10^6$ of the egg white mixture and employing the positive pole, no erythema was observed. Few papules appeared on the margin outside of the treated area. These papules were due to the extra pressure of the metal electrode. This test-reaction was recorded as negative.

April 20, 1948: With a $1:10^5$ solution with the positive pole after five minutes, a few papules appeared with slight erythema about them. The papules appeared at the orifices of the sweat glands. A similar reaction was obtained with the negative pole at the end of two minutes, with practically no erythema. The reaction was regarded as faintly slightly positive. The control was negative.

April 13, 1948: A $1:10^4$ solution with the positive pole showed no immediate reaction, but minute scattered discrete papules appeared at the orifices of the sweat glands, the discrete papules fusing so that a confluent wheal was formed. The papules disappeared after thirty minutes. Reaction with the negative pole disappeared within forty-five minutes. The reaction was recorded as slightly positive. The control was negative.

February 10, 1948: With a $1:10^2$ solution and with positive pole, an erythema appeared at once on removal of the electrode, showing a distinct pore pattern within two minutes. There was marked erythema of about 1 cm about the wheal. The size of the wheal corresponded to that of the electrode. With the negative pole the pore pattern was similarly visible after two minutes with a fairly large erythema. The reaction was recorded as moderate. The control was negative.

February 3, 1948: With a $1:10$ solution whealing reaction, an erythema was observed with both poles. This was recorded as a marked reaction. The control was negative.

With the crystalline egg albumin solution, commencing with 1:10,⁵ positive reactions were obtained only with the negative pole; with 1:10,⁴ a large wheal was obtained.

Systemic or Constitutional Reactions.—This patient had two episodes which can readily be interpreted as constitutional reactions following the electrophoresis of the 1:10 and the 1:100 solutions of the 50 per cent egg white-glycerin mixture. About four hours after each electrophoretic test the patient had fever which ranged from 101 to 102 F., with a cough and running nose. The fever lasted one day. The cough and running nose persisted for several days. These experiments were done one week apart.

DISCUSSION

It has been recognized for many years that egg white is a complex mixture of proteins. These are usually classified as ovalbumin, conalbumin, ovamucoid, mucin and globulin. Which of these have been responsible in patients sensitive to egg white has not been explicitly determined on a quantitative basis. On subjecting dilutions of egg white to electrophoretic analysis by the moving boundary method, it was first reported by Young⁹ that five or six boundaries could be seen. Indeed, some of these boundaries seem to be complex, indicating that more than six boundaries were present. On the other hand, egg white in the ultracentrifuge showed one sedimenting boundary, indicating that a complex equilibrium existed. In a more thorough investigation of the problem, the nature of these fractions was studied more completely and the isoelectric points of the various components were determined. These varied in a 0.1 N salt solution in one series of experiments, from approximately pH 4.3 to pH 5.9. The widespread range of the isoelectric points in the mixtures may, therefore, account for the fact that both the positive and the negative poles were effective in producing the skin reactions observed here. For example, at pH 5.4 in the complex mixture there are both negatively and positively charged components. The skin in these experiments, as previously shown for ragweed extract solutions, acts as an electrophoretic fractionation membrane. With the positive pole, the negatively charged constituents are prevented from going into the skin, and vice versa. Thus the egg white system, although similar to the ragweed system in having both poles effective, is nevertheless different because of the electrification of the molecules in the system. It would be desirable to fractionate egg white electrophoretically and study the way in which skin reactivity to the various fractions varies with the nature of the fraction.

In this experiment the crystalline egg albumin reacted positively only with the negative pole. This has not been demonstrated heretofore. It indicates that the chemical purification of this preparation, which did not

show the same reaction as the mixture of egg white, provides a new tool for studying skin permeability in the allergic patient as well as certain immunologic reactions.

CONCLUSIONS

In electrophoresis of a mixture of egg white in 50 per cent glycerin on the skin of a child clinically sensitive, faint positive reactions were obtained with a 1:10³ solution. With stronger solutions of egg white mixture, the skin reactions were also correspondingly stronger until the maximum reaction was obtained with a 1:10 solution. Both the positive and negative poles were effective in producing the skin reactions.

With the crystalline egg-albumin solutions, positive reactions were obtained only with the negative pole. To avoid unfavorable reactions, only the 1:10³ and 1:10⁴ solutions were employed for testing.

On two occasions, systemic or constitutional reactions occurred, commencing four hours after the electrophoresis of the 1:10 and 1:100 solutions of the 50 per cent egg white-glycerin mixture. There was an elevation of temperature and cough and leaking of the nose lasting for one day and several days, respectively.

The purification of egg white may provide a new tool for studying skin permeability in the allergic patient as well as certain immunologic reactions to the fractions obtained.

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450 West End Avenue
(Dr. Peshkin)

INFECTION IN THE ALLERGIC CHILD

BEN F. FEINGOLD, M.D.

Los Angeles, California

BEFORE undertaking a consideration of infection in the allergic child, it is necessary to clarify our understanding of the term "allergy." The great confusion that exists is well expressed by Rich¹⁸ in his text on the *Pathogenesis of Tuberculosis*. "As for the term 'allergy,' that word has become so debauched by indiscriminate usage that it would be fortunate indeed, if it could be dropped completely from the vocabulary of science. It is now applied to such diverse and unrelated types of altered bodily states that it has become a fertile source of confusion and misunderstanding. Some writers use the term 'allergy' to indicate all types of hypersensitivity to foreign antigens, whether bacterial or non-bacterial; others limit the term to particular types of hypersensitivity; others include drug idiosyncrasy, still others apply the term to all changed reaction capacities that result from contact of the tissues with antigens, including not only all forms of hypersensitivity, but also all forms of acquired immunity, whether antibacterial or antitoxic; others write freely of 'physical allergy,' i.e., hypersensitivity to heat, cold, or sun light; and Von Pirquet, who created the word finally in his last monograph on the subject ('Allergie des Lebensalters') extended its meaning to embrace even the general bodily changes that occur with advancing age, and which favor the development of malignant tumors. To extend the meaning of the word 'allergy' to include every conceivable sort of bodily change, simply robs the term of all possible usefulness and creates the most unfortunate confusion; and this especially since those who use the term rarely take the trouble to state clearly the particular meaning which the word holds for them."

The term "allergy" has become so deep-rooted in both scientific and everyday usage that to delete it from our language would be an almost impossible task. We are victims of convention, but recognizing this, we apply the term "allergy" to all altered states of tissue resulting from antigen-antibody interaction. The nature of the tissue alteration in great measure depends upon the quality of the antigen evoking the response. Such common allergic syndromes as hay fever, asthma, and eczema are characterized by reversible tissue changes which are activated by non-bacterial antigens which produce increased capillary permeability, edema, smooth muscle,

From the George Piness Allergy Group and the Department of Allergy, Los Angeles Children's Hospital.
Presented at the Fifth Annual Session of The American College of Allergists, April 14-17, 1949, Chicago, Illinois.

stimulation, and increased activity of glands. These responses are in striking contrast to the fixed changes resulting from death of tissues which are the consequences of the action of bacterial antigens upon susceptible tissue. With tissue destruction there is no restitution. On the basis of fixed tissue responses such seemingly diverse clinical entities as *rheumatic fever*, *glomerulonephritis*, *periarteritis nodosa*, *lupus erythematosus*, *dermatomyositis*, and *post infectious encephalitis* are currently attributed to the phenomena of allergy.

There are immunological differences between the two types of tissue responses. In the reversible or non-bacterial type of tissue hypersensitivity the skin test is characterized by an immediate whealing of short duration; antibodies are present in the circulating blood which are demonstrable only by passive transfer or biological tests; and *in vitro* contact of hypersensitive cells with a specific antigen does not produce death of cells. In the non-reversible or bacterial type of tissue hypersensitivity the skin test reaction is delayed like the tuberculin test; antibodies in the circulating blood are demonstrable *in vitro* as precipitins or agglutinins; passive transfer is not possible, and *in vitro* contact of hypersensitive cells with a specific antigen produces death of cells.

Appreciating that the tissue response in a hypersensitive organism is determined by the quality of the antigen, we recognize that non-bacterial substances, such as pollens, epidermal factors, and foods evoke reversible tissue changes and distinct immunological phenomena which explain the symptomatology of such common diseases of the clinic of allergy as hay fever, asthma, and eczema; while bacteria and bacterial products assert themselves in fixed tissue reactions with different immunological responses which are clinically identified with *rheumatic fever*, *glomerulonephritis*, and the collagenous diseases. Acknowledging the distinct difference in tissue response to the two types of antigens, we do not accept either bacteria or bacterial products as the etiological agent of such conditions as hay fever, asthma, or eczema whose symptoms result from reversible tissue changes.

What adds to the confusion in recognizing the etiological agent in allergy is the additional factor of the ability of infection to influence the course of existing allergy without any participation on the part of infection in the underlying allergic tissue changes. In other words, infection plays a dual role in tissue hypersensitivity. First, infection may produce fixed tissue changes in the hypersensitive organism and, second, it may influence the course of existing allergy.

When infection does influence the course of existing allergy, it produces a distinct pattern for the allergy. The pattern observed is

one of two types, the type being determined by the nature of the infection. The first pattern (Fig. 1) is observed in association with pertussis, measles, chickenpox, mumps, Kaposi's disease, roseola infantum, and the epidemic viral diseases. With these diseases,

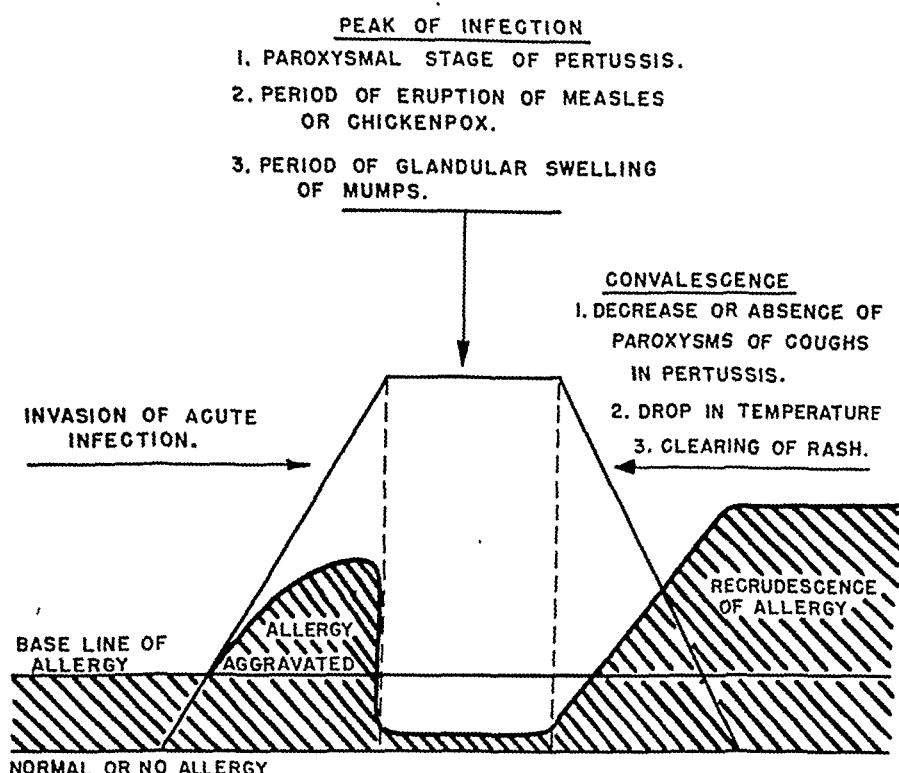


Fig. 1.

during the prodromal stage or period of invasion there is an aggravation of the pre-existing allergy. The symptoms presented during this period will usually be determined by the patient's previous complaint so that the child with allergic rhinitis will have more severe nasal symptoms; the asthmatic child will suffer with asthma or allergic bronchitis; and the eczematous child will present an aggravation of his eczema. As these acute processes approach their full development, the symptoms of allergy become less severe, so that at the fastigium of the disease the child will be free of symptoms of allergy. The nose will be clear; the lungs will be clear; the skin will be clear. Actually, at the peak of these infections the level of allergy is less than prior to the invasion of the acute infectious process. This period corresponds to the paroxysmal stage of pertussis, the exanthem of measles, the eruption of chickenpox, the vesiculation of Kaposi's disease, and the fever of epidemic viral diseases. With convalescence there is recrudescence of the allergy. With convalescence the allergy may recur, and when it does recur it may appear with greater severity and greater intensity than

existed prior to the onset of the acute infectious process. A new base line for the allergy is established, so that the child with mild symptoms of allergic rhinitis may complain constantly of nasal distress; the asthmatic child may have persistent pulmonary findings,

ACUTE UPPER RESPIRATORY INFECTION

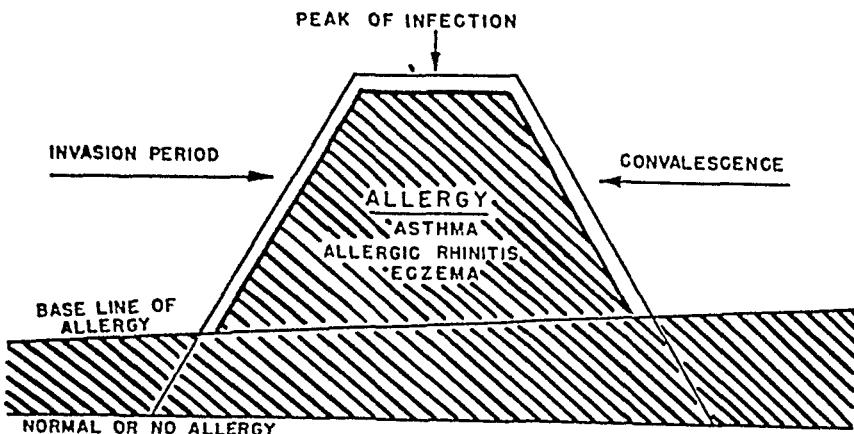


Fig. 2.

or in some instances experience his first attack of asthma; the eczematous child will show an aggravation of his rash.

The second pattern (Fig. 2) is observed most commonly in association with acute infection of the upper respiratory tract, that is, rhino-pharyngitis, acute tonsillitis with or without adenitis, adenoiditis, sinusitis, acute otitis, or any combination of involvement of the upper respiratory tract. With these infections there is no apparent change in the degree of the allergy during the period of invasion, but at the height of the infection there is an aggravation of the allergy. Corresponding to the peak of the infection, the allergy is most severe. The child with allergic rhinitis will have severe nasal symptoms, the asthmatic child will suffer with severe asthma or allergic bronchitis, while the rash of eczema will be aggravated or itching is frequently more intense.

DISCUSSION

An analysis of some of the observations and attitudes on infection in the allergic child expressed in the literature in comparison with the two patterns presented raises some interesting points for discussion.

The exacerbation of allergy by measles is mentioned by Peshkin,¹² who observed that asthma frequently recurred or was aggravated during the incubation period of measles, but with the appearance of fever the asthma cleared in the majority of these patients.

No other such observations has been noted in the literature. The lack of further reports on the exacerbation of allergy during the invasion of an acute infectious process can perhaps be explained by its failure to occur as a constant finding. As the degree of aggravation of the allergy during this phase of the acute infectious process is usually not as severe as that seen following the disease, the clinician may overlook this observation unless he is alert to the over-all pattern produced by an acute infectious process in the allergic child. In some cases, during the invasion of a contagious disease, the symptoms of allergy may return with greater violence and fail to respond to the usual medical management. With the establishment of the fastigium of the disease the symptoms of allergy disappear completely. This observation is not peculiar to children. A woman, aged thirty-seven, whose asthma of many years' standing was controlled with a pollen antigen, had a sudden recurrence which persisted for ten days, when it cleared with equal suddenness. The cough present since the onset of the asthma increased in severity and became paroxysmal. During this stage the chest was clear. The blood count revealed 12,000 leukocytes with 44 per cent polymorphonuclear leukocytes, 54 per cent lymphocytes, and 2 per cent monocytes. The diagnosis was pertussis. Similar history was experienced in a woman, aged twenty-eight years, whose asthma was under control. For one week prior to the establishment of clinical signs of parotitis the patient experienced a severe attack of asthma. Concomitant with the swelling of the parotid glands, the asthma cleared.

Improvement of the signs and symptoms of allergy at the peak of an acute infectious process is also reported in the literature. Very early in the history of clinical allergy, Von Pirquet observed that a positive tuberculin may become negative during measles. In a discussion of desensitization, Rich¹⁸ also points out "that the cutaneous reactivity to tuberculin often diminished markedly during the early stage of the exanthem of measles, to return again after a week or two. A similar diminution in reactivity has been observed during other acute infections." The clearing of eczema with measles is a common clinical observation. We have already noted Peshkin's¹² observations that asthma cleared with the appearance of fever of measles. Very little note has been made in the pediatric literature of the very important observation that a positive tuberculin becomes negative during the paroxysmal stage of pertussis,¹ which was reported by Galli,⁹ Pospischill,¹⁴ Hamburger,¹⁰ and Reiche¹⁷ and others,^{2,3,11,13} at about the same period that Von Pirquet reported on the tuberculin response during measles. The writer has questioned many clinicians, both pediatricians and allergists, and none can recall the occurrence of asthma during the

INFECTION IN THE ALLERGIC CHILD—FEINGOLD

paroxysmal stage of pertussis. Rackemann¹⁵ states that when allergy is well established the effect of an intercurrent infection will depend upon its severity. An acute infection of relative severity he states may alleviate the allergy temporarily. The allergic

MEASLES ECZEMA—ALLERGIC DERMATITIS ASTHMA

PATIENT: M.S., 18 MOS.

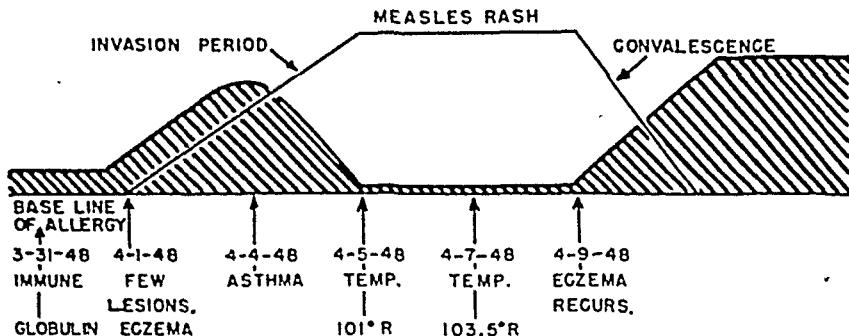


Fig. 3.

MEASLES ECZEMA — ASTHMA

PATIENT: L.J.: AGE. 4 YRS.

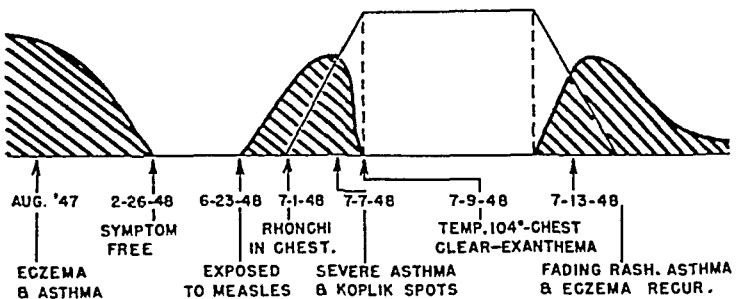


Fig. 3a.

child who gets measles will lose his eczema or asthma at the time of the intercurrent disease. Rackemann's opinion differs from our experience. The influence upon the allergic state is not related to the severity of the infection but to the nature of the infection. The acute infectious diseases, measles, mumps, chickenpox, and pertussis will show an improvement in the allergic state at the peak of the infectious process without relation to the severity of the infection.

In Figure 3, illustrating eczema influenced by measles, the

child suffered a modified measles following the administration of immune globulin. In Figure 3a, illustrating the influence of measles on the course of asthma, the child suffered with a severe reaction to his measles, but during the period of intense eruption

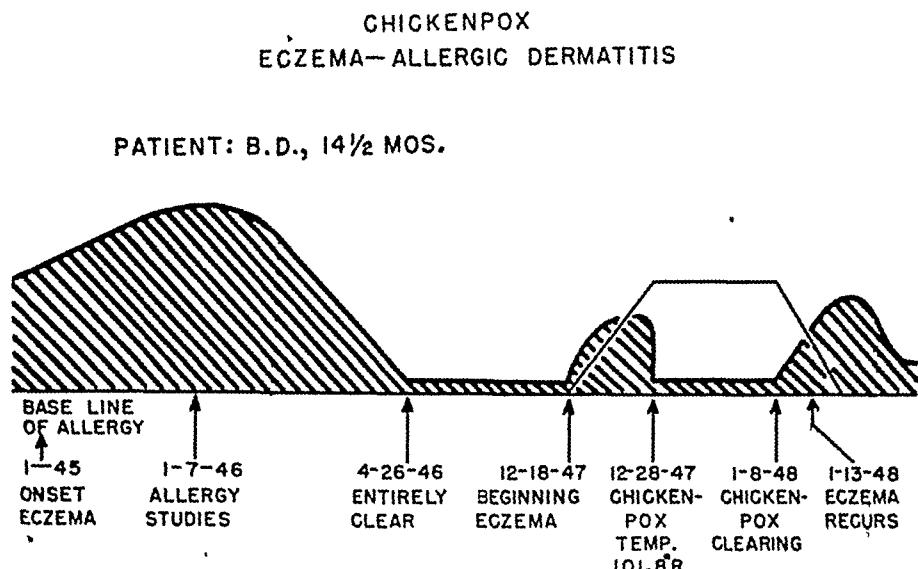


Fig. 4.

CHICKENPOX
ECZEMA — ALLERGIC DERMATITIS

PATIENT: R.D. AET. 4 YRS.

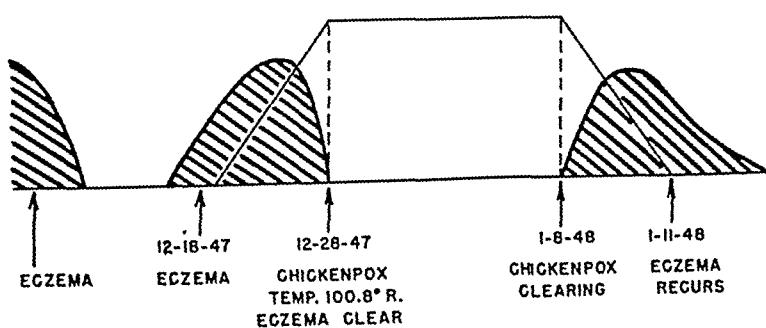


Fig. 4a.

his chest was clear and there were no symptoms of asthma.

In Figures 4 and 4a, illustrating eczema influenced by chickenpox, one child suffered a severe infection with chickenpox while the other child had only a mild infection. These cases serve to illustrate that severity of the infection is not the influencing factor. With the acute infectious processes, regardless of the intensity of the infection, allergy will improve, while in the upper respiratory infections allergy is aggravated at the peak of the infection. Here again, severity of the infection is not the determining factor. This

INFECTION IN THE ALLERGIC CHILD—FEINGOLD

would seem to indicate that the nature of the infection is the influencing factor rather than degree of infection.

The contention that fever is the determining factor when allergy improves during the course of an acute infectious process can be disclaimed by the same argument. During the course of the diseases mentioned in association with pattern 1, clinical allergy will improve without regard to the degree of fever while in severe upper respiratory infections accompanied by high temperatures, as high as 104° or 105°, the allergy may be aggravated. Fever may be a manifestation of an allergic response, as is observed in serum sickness, the classical example of the acute allergic reaction, or, as has been more recently observed, in penicillin reactions.

There is a difference in the immunological responses in the two groups of infections, as is evidenced by the fact that the first group calls forth a leukopenia or lymphocytosis in the blood picture, while the second group evokes a polymorphonuclear leukocytic response. The first-group usually confers an immunity after a single infection while the second group confers no immunity. This immunological difference between the two groups of infections is consistent with the observations reported by Bunting⁵ and also Ehrlich and Harris.⁶ These investigators state: "That the polymorphonuclear leukocyte does not play a part in antitoxic immunity seems to be indicated by a series of clinical observations which have been summarized in a general law of pathology to the effect that no disease which runs its course with a neutrophil leukocytosis is followed by lasting immunity. A high lymphocyte-monocyte ratio suggests resistance."

The aggravation of the allergic state by an infectious process as evidenced by the onset of the first attack of asthma is well recorded in the literature. Practically every modern text on either pediatrics or allergy cites the infectious processes as precursors in the onset of asthma and emphasizes the frequency of pertussis as an exciting agent.

In a study on the incidence and significance of various diseases and infections in asthma in children, Peshkin¹² pointed out the frequency of association of pertussis and measles with the onset of asthma. Walzer²⁰ states that among the common contagious diseases of childhood involving the respiratory tract, pertussis outstrips all others as an etiologic factor in asthma. Walzer also reports that a number of non-sensitive middle-aged asthmatic patients date the onset of their asthma to the influenza epidemics of the last decade. Bray⁴ observes that at least one out of each three cases of asthma will assign the onset to some infectious disease, and whooping cough and pneumonia are by far the most common. Dienes⁷ states that no doubt at certain times certain changes occur

which predispose to sensitiveness. During infections such as whooping cough, that part of the system which makes antibodies is much more irritable. He believes that sensitiveness frequently follows infections. Rackemann¹⁵ reported a similar attitude when he states that an acute infection irritates that part of the system which makes antibodies. Asthma may often begin after whooping cough, measles, or other acute infections. In reporting on prophylaxis in allergy, Ratner¹⁶ also emphasizes the importance of measles and pertussis in antedating asthma. In a discussion on the etiology of asthma, Tuft¹⁹ indicates the frequency of a history of pneumonia, influenza, or pertussis prior to the onset of the initial asthmatic attack. In his text *Allergy in Theory and Practice*, Cooke⁶ expresses the opinion that "A clinical history of an acute infection especially measles, pneumonia, influenza, or bronchitis as the precursor of an allergy is obtained too frequently to be overlooked or to be rejected as of no moment. Infection as provocateur of an allergy but not specifically and causally related to that allergy is an idea that must be investigated further." Cooke's statement is very pertinent. The infectious processes may not only play a definite role in the causation of clinical allergy, but as illustrated by Pattern 1 may have a distinct influence upon the course of the allergy. The occurrence of clinical allergy following an acute infectious disease is only one phase of the interplay between allergy and the acute infectious processes. The influence of the infectious processes upon the course of allergy raises many problems for investigation. Why is the alteration in the pattern of the allergic state by the infectious processes not a constant manifestation? In some cases the aggravation of the allergic state during the period of invasion may be observed with no recrudescence during or following convalescence. On the other hand, the exacerbation of clinical allergy following an acute infectious process may occur without any apparent influence upon the allergy during the phase of invasion. That this clinical observation is not uncommon is implied by the literature, which frequently mentions the acute infectious processes as precursors of clinical allergy. The only constant observation is the improvement of the allergic state during the fastigium of the infectious diseases. Correlation of these clinical observations with immunological studies would no doubt reveal the answers to some of these clinical phenomena.

The aggravation of the allergic state by the acute respiratory infections is generally accepted in pediatric practice and is cited frequently in the literature by observers reporting on infection in allergy. The allergy is most severe at the peak of acute infection (Fig. 5). The allergic symptoms in association with this type of infection do not respond to the usual medical management for

allergy. The best response is observed following the use of antibiotic drugs, either sulfonamides or penicillin. As the infection subsides, the symptoms of allergy improve without any specific therapy directed toward the allergy.

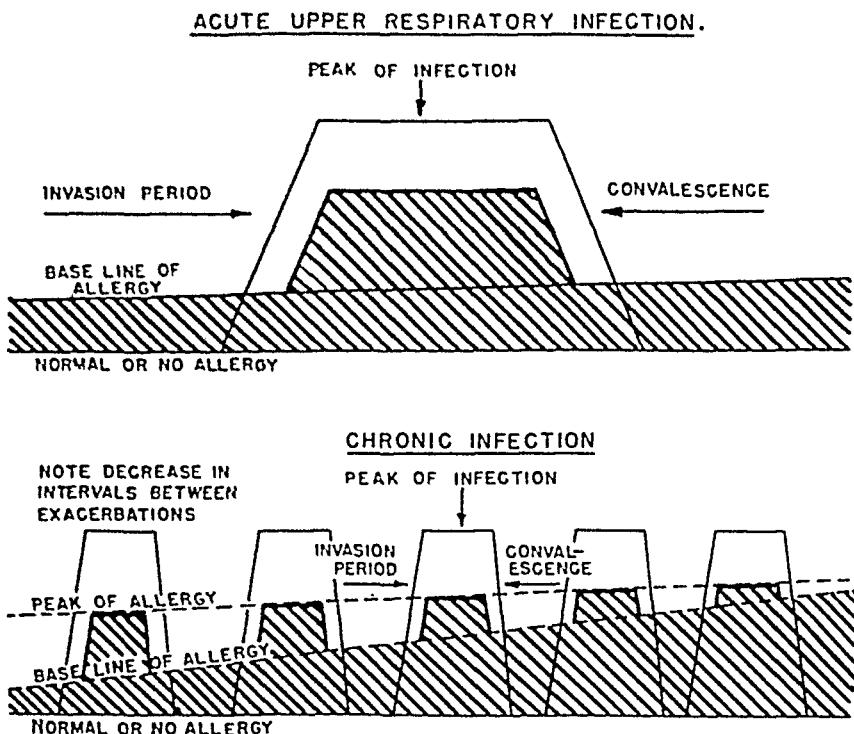


Fig. 5.

In chronic infection of the upper respiratory tract, which includes all chronic infections of the lymphoid tissue of the nasopharynx, the tonsils, adenoids, sinuses or cervical nodes, and in lymph node infection secondary to infected allergic dermatitis, a pattern similar to that just described for allergy in association with acute infections of the upper respiratory tract is observed (Fig. 5). Chronic infection is merely a repetition of the pattern seen in association with acute infection of the upper respiratory tract. During the interval the patient has symptoms of allergy of a varying degree. With each acute flareup of the infection as treatment is directed against the infection, the allergy shows a definite improvement by returning to what is apparently its former level. These children present a great degree of periodicity. They offer a history of acute exacerbation of both the infection and the allergy at regular intervals. This periodic recurrence of the acute symptoms presents a cyclic pattern with a free interval between attacks varying with the individual patient from several weeks to several months. As has been mentioned, during the acute period of the

infection the symptoms of allergy are aggravated but improve as the acuteness of the infection subsides. If one carefully reviews the history of these cases for a period of many months or, in some instances, several years, it will be observed that there is a gradual increase in the level of the residual allergy so that with each succeeding attack of acute infection there is an increase in the severity or intensity of the allergy. Eventually following repeated attacks of acute infection the child's allergy may reach a level which practically incapacitates him. This is the child who comes to the pediatrician or allergist offering a history of a mild allergy at the onset, with frequently recurring infections followed by a gradual increase in the intensity of the allergy. As a result of the severity of the symptoms, that is, of both the infection and the allergy, these children usually present a marked degree of impaired nutrition. They are pale, wan-looking, with deeply circled eyes giving them the expression we refer to as the "allergic facies." They offer the appearance of being markedly anemic, but a blood picture usually shows the absence of any anemia.

Early in the development of this particular pattern, the acute exacerbation of infection responds extremely well to specific therapy with the antibiotics. With recovery from the acute infection, the co-existing allergy improves. It is this particular response of the allergy, following the use of antibiotic drugs which are directed against the infectious process, that leads many pediatricians and, for that matter, many allergists, to consider bacterial sensitivity as the underlying cause of the signs and symptoms in this group of children. But such reasoning does not take into consideration the fixed tissue changes which characterize the pathology of hypersensitive tissue in response to infection, nor the clinical observation that the signs and symptoms of allergy are present during the interval between acute exacerbation of the infection. The allergy may be less severe but it is constantly present. The nasal mucosa is still edematous, the turbinates are still swollen, there is still considerable discharge from the nose with post nasal drip producing cough. The lungs during the interval may reveal rhonchi and some wheezing. All these findings may be present during the interval between attacks, but during the acute phase of the infection they become aggravated because of the influence of infection upon existing allergy.

Further clinical evidence for such reasoning is the observation that a child who offers a history of allergy with recurrent upper respiratory infections will show a definite control of his allergy when under competent allergy management. In other words, a child may have an upper respiratory infection but it is not accompanied by the symptoms of allergy when his allergy is con-

trolled. That a relationship exists between infection and allergy is evidenced from the patterns observed. The infectious diseases have a definite influence upon the clinical picture of allergy in childhood; yet one would not accept either pertussis, chickenpox, measles, or mumps as part of the etiology of allergy. Similarly, because upper respiratory infections influence the existing allergy, they should not be considered the etiologic factor of the allergy. The co-existence of allergy and infection does not necessarily mean bacterial sensitization. That the relationship between infection and allergy acts in both directions is evidenced first by the absence of the allergic symptoms in the presence of upper respiratory infection when the allergy is under control through treatment, and second, by the decrease in the severity and incidence of upper respiratory infections when the allergy is under control.

As has been indicated, following each exacerbation of a chronic infection the allergy may return to a somewhat higher level than existed prior to the onset of the acute symptoms of infection. Eventually, after repeated acute attacks of the infection, a level is reached at which the influence of the infection upon the allergy is so great and the base line for the allergy is so high, that even specific therapy directed against the infection influences the allergy very little, if at all. What is further interesting, in this particular state specific therapy directed against the allergy often has little influence on the allergy. It will be observed that these children frequently present a marked degree of sensitivity and their tolerance for even very weak dilutions of antigen may be extremely poor. Successful management in this type of patient is contingent upon (1) eradicating the foci of infection, and (2) instituting competent management for the allergy.

The most frequent focus of chronic infection in the child is in the upper respiratory tract. In this group of children, it is a common error for the clinician to direct his attention toward clearing the infection without specific management for the allergy. This practice occurs quite frequently because following the removal of the foci of infection the condition of the child may improve so markedly that he is not only free from complaints of infection but the symptoms of allergy also clear up. He may be free from symptoms of allergy for a considerable period of time. It is quite important, however, that this group of children, especially those who have had a tonsillectomy or adenoidectomy, should receive immediate, intensive, and intelligent management for their allergy. It is only through such management that one can hope to prevent the recurrence of the factor of chronic infection which complicates the allergy. If the child fails to receive adequate management for his allergy, there is a greater likelihood that the

lymphoid structures of the upper respiratory tract will show hyperplasia with ultimate chronic infection followed by a return of the picture which has just been described for allergy with chronic infection. Once infection sets in again the pattern is repeated, and when the pattern is repeated the management is extremely difficult because controlling the infection in the lymphoid structures which have regrown presents problems which tax the ingenuity of the rhinolaryngologist, the pediatrician, and the allergist.

The recognition of the patterns that occur with infection in the allergic child suggests many clinical applications:

1. The aggravation of the signs and symptoms of allergy after exposure to an acute infectious disease should suggest the prodromal stage of the acute infectious process.
2. The sudden abatement of the allergic symptoms immediately precedes the eruptive stage of measles and chickenpox or the parotitis of mumps. With a history of exposure to either chickenpox or mumps this observation should be particularly valuable in the diagnosis of these diseases where no diagnostic findings precede either the rash or parotitis.
3. The sudden improvement in acute asthma or allergic bronchitis with a persistence or aggravation of the cough should suggest pertussis as a likely complication.
4. In measles, the asthma or allergic bronchitis will clear just before the exanthem appears. The cough persists and is very harassing. At this stage the exanthem may not be typical. The clearing of the allergy and a persistence of cough should suggest the period immediately before the exanthem when measles is suspected.
5. Following an acute infectious disease, an aggravation of the allergy can usually be anticipated. This may occur during clinical convalescence or a few days to several weeks following clinical convalescence. Perhaps in some cases clinical and immunological convalescence do not parallel.
6. If the allergic state is aggravated following pertussis and the acute infectious diseases, then it should be exceedingly important to protect the allergic child against such diseases. For pertussis it means adequate immunization, and for measles, protection with immune globulin.
7. The cyclic character of the acute exacerbation of chronic infection in the allergic child has been indicated. This should be differentiated from the cyclic picture encountered in the recurrent acute allergic state without infection. In the allergic state, uncomplicated by infection, periodicity may occur with or without fever. In the absence of fever, the patient presents the usual signs and

INFECTION IN THE ALLERGIC CHILD—FEINGOLD

symptoms for his allergy. In the presence of fever in the allergic state without infection, a cyclic pattern of two types may be observed.

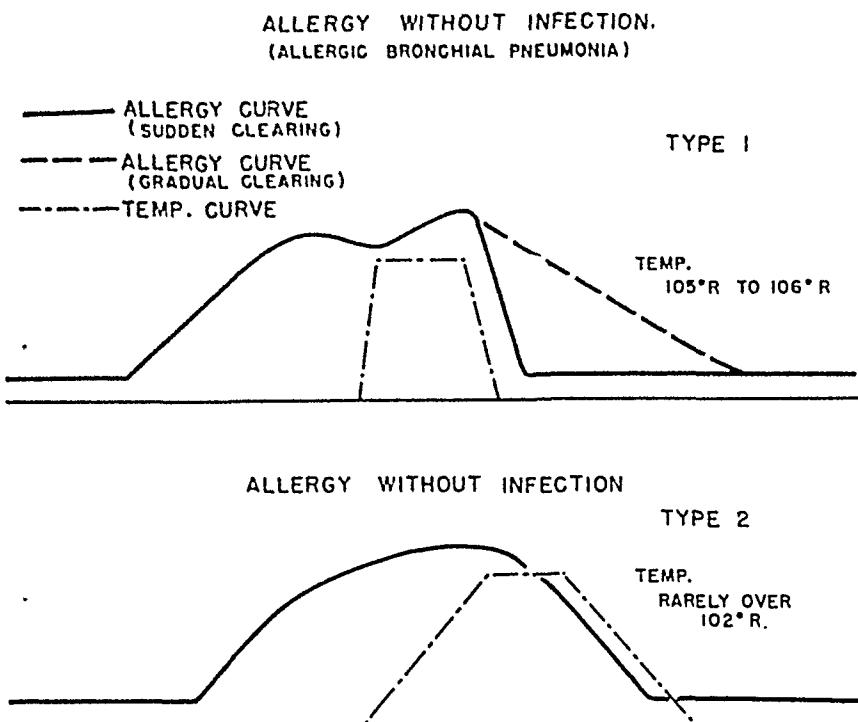


Fig. 6.

ALLERGY WITH INFECTION OF THE UPPER RESPIRATORY TRACT ACUTE OR CHRONIC

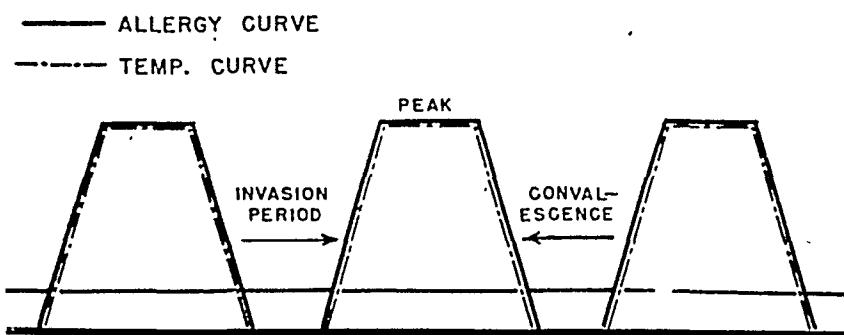


Fig. 7.

- (a) The first syndrome is ushered in by the usual upper respiratory tract symptoms of sneezing, rhinorrhea, and stuffiness of the nose followed by cough and the signs and symptoms of asthma or allergic bronchitis. When sudden high fever— 105° to 106° —occurs during the course of the asthma or the allergic

bronchitis, it usually means the complication of allergic bronchopneumonia. The recognition of this pattern is important in the management of the patient, as a dramatic response may be observed following the early administration of adrenalin and fluids.

(b) The second picture presents the signs and symptoms of acute asthma or allergic bronchitis, which disappears with the sudden onset of fever. Fever in these cases is rarely over 102° orally as compared to the very high fever of 105° or 106° observed in allergic bronchopneumonia.

Fever ushers in the acute state, in the syndrome of upper respiratory infection plus allergy. The occurrence of fever at the onset of the acute picture should serve as a diagnostic guide in the differentiation from allergy without infection. In the latter, fever occurs after the signs and symptoms of acute allergy are fully developed. This observation can also serve as a guide in the management of these children. In the presence of infection the best response is observed with antibiotic medication. In the absence of infection the usual management for allergy is recommended.

SUMMARY AND CONCLUSIONS

1. Infection plays a dual role in allergy. First, it may participate in tissue hypersensitivity of the fixed tissue variety; and second, it may influence the course of existing allergy.
2. When infection influences the course of existing allergy, it produces one of two patterns depending upon the nature of the infection.
3. With the infectious diseases—pertussis, measles, mumps, chickenpox, roseola infantum, Kaposi's disease, and the epidemic viral infections— allergy is always improved at the peak of the infection.
4. Upper respiratory tract infections aggravate allergy at the peak of the infection.
5. Chronic infection is a repetition of the second pattern presented.
6. Management of allergy with chronic infection usually necessitates clearing the foci of infection and competent treatment for the allergy.
7. Some clinical applications of the patterns presented have been indicated.

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672 So. Westlake Avenue

BRAZILIAN SOCIETY OF ALLERGY

The program of a symposium and plenary session of the Brazilian Society of Allergy, which was held at the Polyclinic, Rio de Janeiro, November 6-11, 1950, arrived as this issue went to press. The following are the officers of the Society: Nelson Passarelli, President; E. Brum Negreiros, Vice President; Haroldo Cardoso de Castro and Newton Guimaraes, Secretaries; Sayao Lobato, Treasurer; and Mario Miranda, Librarian.

The first symposium, on urticaria, was presided over by Prof. Dr. Ramos e Silva. The symposium on eczema was conducted by Prof. Dr. Francisco Eduardo Rabello, on asthma by Prof. Dr. Luiz Capriglioni, and on neuropathic allergies by Prof. Dr. Deolindo Couto. The last two days of the convention were taken up with the plenary session.

THE INTRAMUCOSAL TEST AND A COMPARISON OF ITS REACTIVITY WITH THE INTRADERMAL AND CONJUNCTIVAL REACTIONS

HYMAN SHERMAN, M.D., F.A.C.A., and LOUIS A. FELDMAN, M.D.
Brooklyn, New York

THE purpose of this investigation was to study the nature of the intramucosal reaction and to compare quantitatively the intramucosal test with the ophthalmic (drop) and intracutaneous tests. The ocular conjunctiva, which is readily accessible, lends itself easily for such studies.

Dean, Linton and Linton² in 1935 were the first to describe the intramucosal test and the mucosal scratch test. Their work was limited to the nasal mucosa only, and was done in relation to studies in ionization of the nasal mucosa. They found the mucosa to react positively in many cases where the skin tests were negative in patients suffering from allergic rhinitis.

Stevens,⁸ Rudolph and Cohen,¹ Efron and Penfound,³ Peshkin,⁵ and others also used various methods of mucosal investigation, utilizing pulmonary inhalations, cotton pledges in the nose, sprays, powder blowers, and dry pollen in the nose.

Fineman⁴ in 1926 made comparisons of the intradermal, scratch, and conjunctival tests.

Ten patients with hay fever were studied. They consisted of two tree, two timothy, and six ragweed pollen cases. No cases which demonstrated any degree of congestion or dilatation of the ocular or tarsal conjunctiva were accepted for study. All skin titration and ophthalmic tests were performed outside the pollen seasons. Five patients had received or were receiving pollen extract treatment; the other five patients had never received treatment.

TECHNIQUE

The tests were performed in the ocular conjunctiva just below the cornea. (Fig. 1). At first a 1 per cent pontocaine solution was used as a topical anesthetic. This did not cause dilatation of blood vessels of any importance nor did it interfere with the results obtained. Most of the cases received no topical anesthesia.

Using a 26-gauge needle, $\frac{3}{8}$ inch long, and the standard testing syringe, a tiny bleb containing 1/50 cc of testing material was raised in the ocular conjunctiva of one eye. The other eye was utilized for making comparative tests with the drop method.

Presented at the Fifth Annual Meeting of The American College of Allergists, April 14-17, 1949, Chicago, Illinois.

From the Department of Allergy and the Department of Ophthalmology, Jewish Hospital of Brooklyn, N. Y.

DESCRIPTION OF THE INTRAMUCOSAL REACTION

The reaction developed rapidly. There was an immediate injection and dilatation of the conjunctival and scleral vessels about the test site. The injected vessels had a definite violaceous color. The injection and dilatation



Fig. 1. Appearance of eye prior to intramucosal test.



Fig. 2. Control reaction after ten minutes, fading fast.

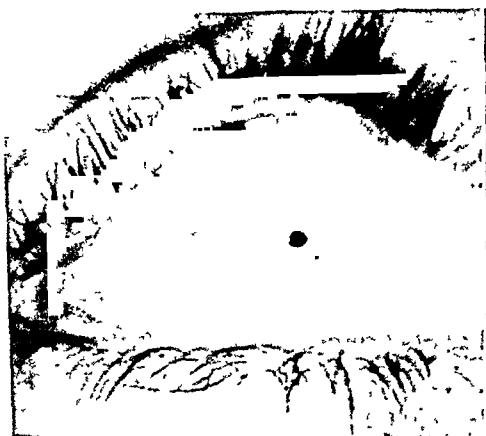


Fig. 3. Reaction after seventeen minutes, showing edema.



Fig. 4. After drop of epinephrine.

of the vessels increased rapidly, spreading nasally, temporally, and downward involving the caruncle and lower lid. (Fig. 3). Edema and itching were present to only a slight extent. Occasional associated symptoms were slight burning, a sensation of fulness in the eye, and slight tearing of the tested eye. There was usually a clear area between the ciliary ring of vessels, which almost always developed, and the area of dilated vessels below or at the test site. The reaction attained its height in six to ten minutes, and began to fade after twenty to thirty minutes. In the stronger reactions there was a wider and more intense injection and dilatation of the blood vessels and increased edema, which extended down to the lower

lid, and in severe reactions down to the malar eminence (Fig. 3). In the mild reactions the local effect of one drop of epinephrine (1:1000) was rapidly effective on the dilated and injected vessels and the edema (Fig. 4). Epinephrine did not shrink the stronger reactions completely, which as a rule needed a second drop.

CONTROL STUDIES

It was desirable to determine the reactivity of the bulbar conjunctiva after testing with a saline control in an allergic subject. Upon the introduction of 0.02 cc of a buffered saline solution there was an immediate injection of the finer and smaller vessels of the bulbar conjunctiva, which reached its height in about five minutes. There was no involvement of the larger blood vessels, as occurred in the specific type of reaction. The violaceous appearance of the specific reaction was present, but to a lesser degree. The intensity of the reaction was far less than that produced by pollen. The reaction seldom exceeded $\frac{1}{2}+$, reached its height in five minutes, and usually faded in ten minutes (Fig. 2). There was no itching or edema. The shrinking effect of epinephrine upon the control was more pronounced than in the specific reaction. The results were identical in five control subjects studied. Control studies were also done in nonsensitive cases, using timothy and ragweed extracts instead of saline. The reactions were of a similar character, and in no instance did the pollen control in the same individual exceed that of the saline control or vice versa.

COMPARATIVE STUDIES OF OPHTHALMIC AND INTRACUTANEOUS REACTIONS

Threshold intramucosal reactions were compared with simultaneous threshold intracutaneous reactions where possible in each patient studied. In the five patients threshold conjunctival reactions were also obtained in the other eye, using the drop technique at the same sitting. In the other five patients the conjunctival tests were obtained one to two months prior or at a later date.

The results of these comparative studies are shown in Tables I, II, III and IV. In each of the ten cases studied, the intramucosal response was greater than the corresponding intracutaneous test. In six of the cases the difference in reactivity was pronounced. Comparisons of intramucosal threshold reactions were also made in each case with the ordinary conjunctival test, using the drop method. The comparative results demonstrate that the intramucosal test is ten to one hundred times more sensitive than the corresponding intracutaneous test. A comparison of intracutaneous thresholds and conjunctival (drop) thresholds indicates that the intracutaneous test is from ten to one hundred times more sensitive than the ordinary conjunctival (drop) test (Table V). These latter findings confirm the original work of Fineman,⁴ and of the author⁶ in the comparative reactivity of the skin and of the conjunctiva.

INTRAMUCOSAL TEST—SHERMAN AND FELDMAN

TABLE I. A COMPARATIVE STUDY OF THRESHOLD REACTIONS

Case No.	Type of Case	Rec'd Treatment	Titrations	D F	00001	0001	mg 0005	N 001	per 005	cc .01	.1	Result
1	R A G	no	Intramucosal Intradermal Eye (drop)	1		12 4		8 0	12	1		✓ X
2	T I M	yes	Intramucosal Intradermal Eye (drop)			8 1		6	10	1		✓ X

Values—1 + Reaction = 4
 2 + Reaction = 8
 3 + Reaction = 12
 4 + Reaction = 16

✓ = Greatest response.

X = Least response.

TABLE II. A COMPARATIVE STUDY OF THRESHOLD REACTIONS

Case No.	Type of Case	Rec'd Treatment	Titrations	D F	00001	0001	mg 0005	N 001	per 005	cc 01	.1	Result
3	T R EE	yes	Intramucosal Intradermal Eye (drop)							8 0 0	4 1	✓ X
4	R A G	no	Intramucosal Intradermal Eye (drop)	1	8 4	6 0		8 0	10	12 3		✓ X

Values—1 + Reaction = 4
 2 + Reaction = 8
 3 + Reaction = 12
 4 + Reaction = 16

✓ = Greatest response.

X = Least response.

TABLE III. A COMPARATIVE STUDY OF THRESHOLD REACTIONS

Case No.	Type of Case	Rec'd Treatment	Titrations	DF	00001	0001	mg 0005	N 001	per 005	cc 01	.1	Result
5	R A G	yes	Intramucosal Intradermal Eye (drop)	1		2 3	8	7 0	12	2		✓ X
6	R A G	no	Intramucosal Intradermal Eye (drop)	1 4		6 4		8 0		2		✓ X
7	T I M	yes	Intramucosal Intradermal Eye (drop)	2 1		8 4		6 0	10	16 2		✓ X

Values—1 + Reaction = 4
 2 + Reaction = 8
 3 + Reaction = 12
 4 + Reaction = 16

DISCUSSION—SLIT-LAMP STUDIES

Some of the specific reactions and control reactions were observed under the slit lamp. The findings corroborated those found on gross inspection using the magnifying 100p.

The intramucosal reaction developed instantaneously and reached its height sooner than did the intradermal or conjunctival test, using the drop method. It is a more diffuse type of reaction than that obtained with the drop technique, which is more localized. However, the subjective

INTRAMUCOSAL TEST—SHERMAN AND FELDMAN

TABLE IV. A COMPARATIVE STUDY OF THRESHOLD REACTIONS

Case No.	Type of Case	Rec'd Treatment	Titrations	D F	00001	0001	mg 0005	N 001	per 005	cc .01	.1	Result
8	R A G	no	Intramucosal Intradermal Eye (drop)	3 1	9 3	6		12 0				✓ X
9	R A G	no	Intramucosal Intradermal Eye (drop)		5 3	9 5 0		7 0	1			✓ X
10	T R EE	yes	Intramucosal Intradermal Eye (drop)						12 7 2	14		✓ X

TABLE V. COMPARATIVE REACTIVITY OF TESTS

Type of Titration	Comparative Response		
	1—10	10—100	100—1000
Intramucosal	—	—	—
Intradermal	—	—	—
Eye (drop)	[REDACTED]		

symptom of itching appears to be more characteristic of the conjunctival pollen test, even in threshold reactions. It was invariably absent in the average intramucosal reaction.

In the specific intramucosal reaction there was a suggestion of corneal dullness resembling edema which could not be seen on gross inspection.

The larger conjunctival vessels were invariably dilated and engorged in the specific intramucosal reaction. In the control studies, using both saline and pollen solutions, the larger conjunctival vessels were not involved in the reaction.

The topical effect of epinephrine was likewise observed under the slit lamp. There was a rapid shrinking of the fine and large vessels, with a consequent diminution of the edema and blush. The epinephrine effect in the specific reaction was much slower than in the control reaction or in the specific conjunctival reaction using the drop method. Edema appeared to persist longer in the specific intramucosal reaction. The shrinking effect of epinephrine on the cornea could be seen in all cases observed.

Fundus studies were negative in all types of reactions. There was no change in lens refraction even in the stronger intramucosal reactions.

Conjunctival titrations are subject to many more technical limitations than are the cutaneous titrations. One great handicap in utilizing the conjunctiva for study is that only two eyes are available in each patient for titration; and good technique does not permit retests of these surfaces at frequent or short intervals. The authors⁷ have previously shown that such a technique is subject to considerable error, especially when used for the purpose of quantitative comparison of eye reactions.

The findings resulting from a comparison of the intradermal and eye (drop) tests re-affirm the conception that the conjunctival test is not a sensitive one and, at best, is a crude index of ophthalmic sensitivity.

SUMMARY AND CONCLUSIONS

Ten patients with various types of hay fever were studied. Intramucosal tests were performed in the ocular or bulbar conjunctiva just below the cornea. The reaction developed very rapidly, attained its height in about ten minutes, and began to fade in twenty to thirty minutes. The reaction consisted of dilatation and engorgement of the fine and larger vessels of the underlying conjunctiva and sclera. In the stronger reactions conjunctival edema and injection of the caruncle developed. The cornea did not appear to participate in the reaction. Slit-lamp studies confirmed these findings. It is noteworthy that itching and lacrimation were absent in these reactions.

A comparison of similar threshold reactions revealed that the intramucosal response is at least ten times greater than the intracutaneous reaction, and at least one hundred times more sensitive than the conjunctival test using the drop method.

Suitable control studies were made.

Practical use of the intramucosal test might be made in clinical allergies where skin tests are negative. However the test is not recommended as a routine diagnostic procedure.

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455 Ocean Avenue

FURTHER EXPERIENCE WITH HISTAMINE IN FOREIGN PROTEIN TYPE REACTIONS

HOMER E. PRINCE, M.D., F.A.C.A., and RICHARD L. ETTER, M.D.

Houston, Texas

SINCE our original report¹ we have continued to use histamine in the treatment of severe foreign protein type reactions and have employed this method of therapy in sixty additional patients. Our experience in treatment of this added number of patients has substantiated our previous impressions concerning the value of histamine for these conditions. Huff² has reported similar results in the treatment of four patients by this method. In addition we have gained further impressions regarding method of administration of the drug, as well as of the clinical behavior of foreign protein type reactions, especially those caused by penicillin.

By far the greatest offender in this series of foreign protein reactions was penicillin. We have not tried to determine the different penicillin preparations, since adequate history or reliable record could not often be obtained. The following table will show the incidence of the offenders:

TABLE I

Penicillin	44
Tetanus antitoxin	5
Estrogens in oil	2
Vitamin B preparations	2
Demerol	2
Immune globulin	1
Poison ivy antigen	1
Chloromycetin	1
Intramuscular liver preparations	1
Undetermined: (liver or penicillin)	1

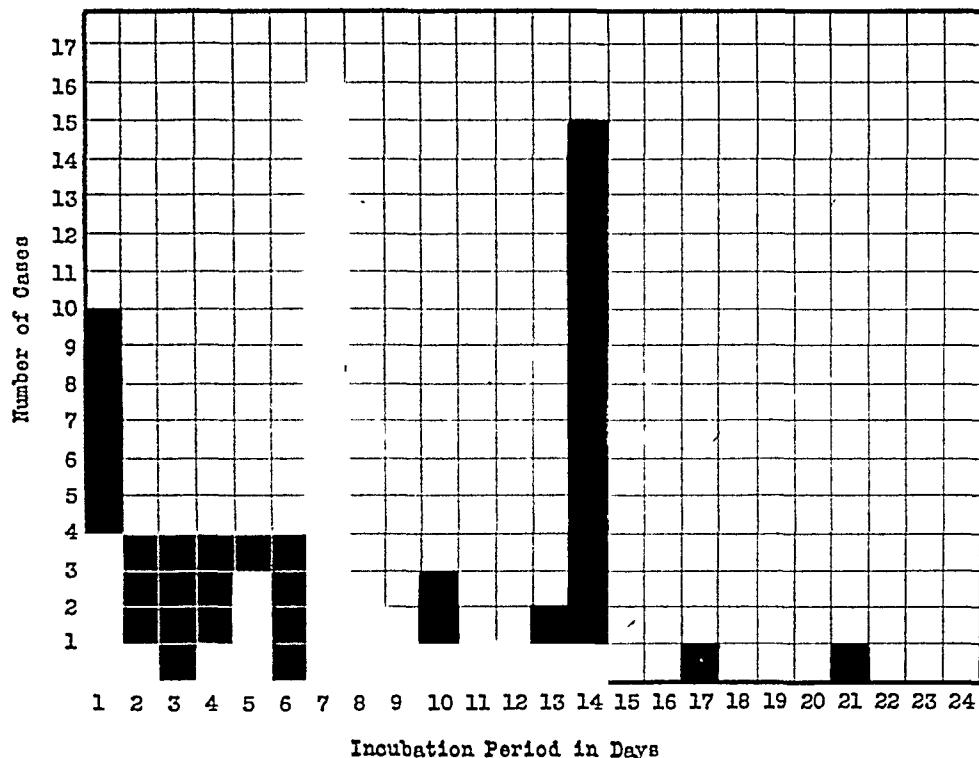
It is of interest to note that the incubation period of the reactions occurred in three distinct groups (see chart). About one fourth appeared as immediate reactions or within about twenty-four hours, another fourth on about the seventh day, and another fourth on the fourteenth post-injection day, while the others were about equally distributed from the second to the twenty-first day.

This pattern of incubation periods very definitely emphasizes a cyclic behavior in the factors determining the foreign protein type reaction. That such a cycle is actually operative is further suggested by occasional relapses in individual patients, or in the persistence of dermatographism or urticaria as a sequel to the reaction; we have observed such relapses or other residual symptoms in some instances to follow a recurring pattern usually of diminishing intensity at periodic intervals.

All patients selected for treatment with histamine had previously been found non-responsive to antihistaminic drugs. Many presented symptoms of great severity including urticaria, angioneurotic edema of variable distribution, itching, temperature elevation, nausea and vomiting, joint pains

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INCUBATION PERIOD OF REACTIONS



and swelling, oliguria, exfoliative dermatitis, abdominal cramps, pulmonary edema, hemorrhagic lesions, "ids," psychosis, injection of sclera, yellow discoloration of the digits, headaches, diarrhea, and fainting. In some instances major symptoms had persisted for a considerable period of time before histamine treatment was initiated.

METHOD OF ADMINISTRATION

Intravenous administration of histamine is the method of choice, in that the dosage can be controlled and undue effects can be terminated upon discontinuation of injection. A dose of 2.75 mg histamine acid phosphate in 250 cc isotonic saline or 5 per cent glucose in water is given for the first infusion to determine the sensitivity of the patient. The rate of the infusion is regulated to just produce a generalized flush; too rapid administration may cause severe headache and substernal pain, while a rate insufficient to bring about flushing of the entire skin is usually ineffective.

At first, we followed the procedure advocated by Horton,¹ giving the infusions twice daily, but we soon discovered that improvement was not uniformly sustained in the interval between infusions. We believe that the average patient does better with injections every four to six hours, in the beginning of treatment. In a few cases of extreme severity, continuous administration has been found necessary. When signs have disappeared,

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or are minimal, the infusions may be reduced to every twelve hours and eventually to every twenty-four hours.

When rapid administration of the above dosage does not produce a generalized flush of the skin, the concentration of histamine acid phosphate may be increased to 1½, 2, 3, or even 4 ampoules, each containing 2.75 mg in 250 cc of diluent. In five cases we have used 6 ampoules and in two instances as much as 9 ampoules in 250 cc of vehicle.

Late in the series of patients comprising our former report the use of intradermal injections of histamine was instituted. We now feel that intradermal injections are sufficient in a great many cases, or may even be the only method available when veins cannot be entered, or in children, as mentioned in our earlier report. Furthermore, while we admit that intradermal injections do not allow control of the response as rapidly as can be accomplished when histamine is given by the intravenous route, we have encountered no instances of undue side effects which we could attribute to intradermal administration.

Titration of a new patient suffering from foreign protein type reaction, to determine his flushing dosage with histamine administered intradermally, affords at once a valuable prognostic clue regarding how difficult he will be to relieve. If a generalized flush can be produced, further injections of the flushing dose are continued intradermally at intervals of four to six hours, in keeping with the clinical response. On the other hand, if the maximum intradermal dose does not produce good flushing, we know that we must proceed at once to intravenous medication, often with a larger dose than 2.75 mg of histamine acid phosphate in 250 cc of diluent. In general, patients who give adequate flushing with smaller doses of histamine seem to improve more rapidly than those requiring the larger amounts.

The titration is made with increasing amounts of histamine beginning with 0.05 cc of the acid phosphate salt, 2.75 mg per cc, or of the dihydrochloride, 1:1,000; if this causes no flushing after about fifteen minutes, 0.10 cc may be tried. If still no flushing is obtained, the 1:100 concentration of histamine dihydrochloride is employed in doses of 0.02, 0.05, and finally 0.10 cc, or occasionally of intermediate amounts when it seems that adequate flushing is imminent and will require only a slight increase in dose.

RESULTS

Many of our patients have been relieved satisfactorily with intradermal injections once or twice daily, so that the treatment could be carried out entirely in the office. Others have required more frequent injections, and these have either been treated at home or have been hospitalized. Quite often, however, particularly in the severe cases, intradermal histamine did not produce sufficient flush to be effective. All such patients have responded to intravenous medication except one who could not be

flushed with 49.5 mg of histamine acid phosphate (18 ampoules) in 500 cc of isotonic saline administered at a rapid rate.

With properly selected flushing dosage of histamine, whether administered intradermally or intravenously, the acute symptoms of foreign-protein-type reactions in fifty-nine of our sixty patients were satisfactorily controlled. The average duration of treatment was about four days. In most instances all but those patients with extremely severe symptoms manifested definite improvement within twenty-four hours, often after the second or third flushing injection. Many of the patients with severe involvement, on the other hand, especially those with extensive angioneurotic edema and joint involvement, required three or four days before improvement was evident, and in some instances additional time was needed for control of the acute symptoms.

Regardless of the severity of symptoms it occasionally happened that the established dose of histamine ultimately caused increased flushing so that the amount had to be reduced. Such decrease in histamine tolerance seemed to occur earlier in instances of smaller dosage requirements than in the relatively more refractory cases, usually associated with more severe symptoms, which responded only to the larger amounts of histamine. This lowering of histamine tolerance impressed us as being a favorable sign indicating clinical improvement.

Occasionally, various antihistaminic drugs and sedatives, such as codeine or demerol, have been employed along with histamine therapy. We have observed no diminution of the flushing response from histamine due to antihistaminic drugs.

We were impressed with one feature of foreign protein type reactions, particularly those due to penicillin: a fair number of these patients, after recovering from acute symptoms of the disease, developed a state of chronic urticaria or dermatographism, usually of low-grade proportions. While further injections of histamine do not seem to help such strictly urticarial complication, the routine allergy management, such as dietary manipulations, eradication of intestinal parasites, and similar measures, has seemed helpful in several of our cases. On the other hand, many of the cases of dermatographism have seemed to respond to continued treatment with histamine, but in a few instances the dermatographism has not been successfully terminated. We do not know whether the urticaria and dermatographism are due primarily to the foreign protein type reaction or whether the reaction has lowered the threshold to the point that previous subclinical factors have become operative.

DISCUSSION

For the mechanism by which histamine affords relief in foreign protein type reactions we offer no theory beyond what might be expected in view of the known physiological action of the drug. It would seem that as capillary dilatation is effected in the skin and subcutaneous tissues or

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in other involved organs or sites, such as joints and periarticular structures, there is set up a process whereby edema lymph and minute traces of antigen deposited in tissue spaces may be returned to the circulatory system for eventual excretion. We have repeatedly observed greatly increased diuresis follow immediately the flushing response to histamine. We have felt that this diuresis, which usually accompanies clinical improvement as manifested by a reduction in local or more generalized tissue swelling, is due more to the mobilization of the fluid element from the swollen areas than to a diuretic action of histamine. On the other hand, it is difficult to say that under certain circumstances histamine does not have diuretic action. The not too infrequent symptom of oliguria associated with severe foreign protein type reactions may indicate that a part of the general reaction has occurred in the kidney parenchyma. Diuresis following adequate flushing with histamine in such an instance would naturally appear to be the result of mobilization of edema fluid from the kidney parenchyma. Horton² has observed the diuretic action of histamine in cases of urinary suppression.

SUMMARY

Sixty additional patients with severe foreign protein type reactions, all of whom had been treated previously with antihistaminic drugs, have been treated with intravenous or intradermal histamine. In all but one case there was clinical improvement. Each patient was considered individually in determining dosage and interval between injections.

Persistent dermatographism or urticaria, usually of low-grade proportions, occasionally follows severe foreign protein type reactions, especially those due to penicillin.

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Medical Arts Building
Houston 2, Texas

Irwin P. Lubowe, M.D., announces the removal of his office to 1 West 85th Street, New York 24, N. Y. Doctor Lubowe is an Associate Fellow of The American College of Allergists, and his practice is limited to dermatology and dermatological allergy.

NETHAPRIN IN THE TREATMENT OF RESPIRATORY ALLERGY

FRENCH K. HANSEL, M.D., F.A.C.A.

St. Louis, Missouri

EARLIER reports have described the beneficial effects of a mixture of Nethamine and Butaphyllamine, with and without phenobarbital, in the treatment of nasal and respiratory allergies.^{1,5} This compound is supplied under the name "Nethaphyl." Recently, a companion product has been made available under the name "Nethaprin," containing 25 mg of Nethamine (methylethylamino-phenyl propanol) Hydrochloride, 60 mg of Butaphyllamine (theophylline aminoisobutanol), and 6 mg of Decapryl (doxylamine) Succinate in each capsule or in each 5 cc (teaspoonful) of the syrup. Nethamine is a sympathomimetic amine with an ephedrine-like action. It differs from other compounds of this group in having little or no pressor action, seldom producing any significant degree of the usual ephedrine side actions, such as nervousness, palpitation or increased blood pressure.¹ Butaphyllamine has the basic action of other theophylline derivatives with the possible advantages of better absorption and toleration.⁸ Decapryl Succinate is an antihistaminic and antiallergic drug with a high milligram potency.² Experimentally, it relaxes bronchioles that have been constricted by histamine.³ The small doses commonly employed at the present time are virtually free from significant side effects.

In the management of respiratory allergy, especially bronchial asthma, drug therapy is employed primarily for the purpose of giving the patient symptomatic or palliative relief. It is, therefore a valuable and indispensable adjunct which must be continued until the patient is free from symptoms.

Our observations on the administration of Nethaprin are based upon two years' experience with 441 bronchial asthma patients. They were given a total of 80,000 capsules and 180 ounces of the syrup, usually in dosage of one or two capsules (or teaspoonfuls) three times daily. The writer followed more than half of these patients personally during the administration of a total of 56,000 capsules and all the syrup. For the remainder of the clinical material he is indebted to collaborating members of the Hansel Foundation who kindly contributed case histories for the study.

As might be expected, the degree of satisfactory response to Nethaprin in bronchial asthma parallels the degree of severity and chronicity of the disease. The response was satisfactory in a large percentage of the chronic cases. Actual degree of relief depended upon the extent of the patient's symptoms as contributed by such complications as emphysema and chronic bronchitis. The milder cases, particularly of the paroxysmal type,

"Nethaphyl," "Nethaprin," "Nethamine," "Butaphyllamine," and "Decapryl" are trademarks of The Wm. S. Merrell Company, Cincinnati, Ohio, from whom clinical supplies for this study were obtained.

RESPIRATORY ALLERGY—HANSEL

responded very satisfactorily. In such cases the relief from each attack was highly gratifying in from 85 to 90 per cent of the cases.

On the whole, the response of therapy with Nethaprin in older children, age eight to twelve years, was most satisfactory. Usually, a single capsule or one teaspoonful of syrup given three times daily was adequate in these cases.

Nethaprin appears to have a synergistic action which tends to neutralize the undesirable stimulating effects sometimes associated with ephedrine-like drugs and theophylline derivatives as well as the depression sometimes associated with antihistaminic drugs, while the three agents, Nethamine, Butaphyllamine, and Decaprym, combine to relieve the allergic and asthmatic symptoms.

Although the usual single, oral dose was one capsule or teaspoonful for older children and two for adults, there is considerable latitude in dosage. Many adults respond well to a single capsule, whereas apparent therapeutic failure has resulted from failure to give three or four capsules to patients not relieved promptly by lower dosage. When therapy was continued over a long period of time, it was not necessary to increase the dose.

Patients with severe chronic bronchial asthma who are subject to attacks of status asthmaticus may develop symptoms of such severity that no form of therapy short of intravenous injections of theophylline will give satisfactory relief.^{6,7} In such instances, oral therapy should not be continued when it does not give relief. After the attack has subsided following parenteral medication, oral therapy should be resumed.

On the whole, the continued use of Nethaprin was found to be dependent upon the age of the patient, the severity of the symptoms, and especially upon the response of the patient to allergic management. As the patients improved under such a program, drug therapy was required less and less frequently and was ultimately discontinued in a large percentage of cases.

SUMMARY

1. Nethaprin has been used over a two-year period in the symptomatic and palliative treatment of 441 cases of bronchial asthma.
2. The effectiveness in the relief of symptoms has been highly gratifying.
3. Untoward side effects were inconspicuous.
4. The usual single oral dose was one capsule or teaspoonful for older children, two capsules for adults, repeated as needed (usually three times daily).
5. Repeated administration has not necessitated an increase in dosage.

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AIR-CONTAMINANT SURVEY OF SANTA BARBARA, CALIFORNIA (1947-1948)

HILDAHL I. BURTNES, M.D., and SONIA E. ALLEN, A.B.
The Sansum Clinic
Santa Barbara, California

INVESTIGATION of the literature shows that there have been several excellent studies of both pollen and fungus contaminants in the air for various areas on the Pacific coast. However, such a study does not appear to have been made in Santa Barbara County, and this survey was undertaken to determine the contaminants present, the abundance of their occurrence, and any seasonal variations.

Pollen studies were made with the emulsion-covered slide, exposure being made on top of a three-story building in the center of Santa Barbara valley. As Santa Barbara lies between the Santa Ynez mountains and the ocean, this seemed a central location. The prevailing wind here is from the south, and the average velocity is about 13 miles per hour. The average rainfall in this area is about 18 inches, although during the two years of this study the total fall each year was less than one-half this amount. The slides were read over a one-inch square surface, after a 24-hour exposure in a sheltered holder, and results were tabulated on a weekly basis. The weekly figures are used, as these give larger and more easily observed differences on both table and graph.

Fungus investigation was twofold, both the slide and plate methods being used. However, the same problem arose that has been encountered elsewhere in this connection—no correlation being found between the slide and the plate counts. Although both are recorded, the plate count seems the more reliable in that many of the colonies are not identifiable on the slide, while only the rusts and smuts fail to grow on the plates. Standard petri dishes were used, being covered with Sabouraud's agar the first year and the special medium being used in the national fungus survey the second year. The plates were exposed on a shelf extending out from the second-story window ledge on the west side of the same building where the slides were exposed. Again results are tabulated on a weekly basis, the daily exposure being 12 minutes in the early morning.

Two facts stand out in the pollen study. First, the abundance of pollen in the spring is very marked here, due largely to *Quercus* and *Pinus*, supplemented the first year at least by a very large *Cupressus* showing. Although neither *Pinus* nor *Cupressus* is found to be the chief cause of hay fever in many cases, the volume here makes them significant, especially as they fall so near the period of the more frequently troublesome *Quercus*. In contrast to other areas, the fall count is very low; in fact, the low count of ragweed is surprising in the light of the known area of ragweed stands in this county. No attempt has been made to correlate

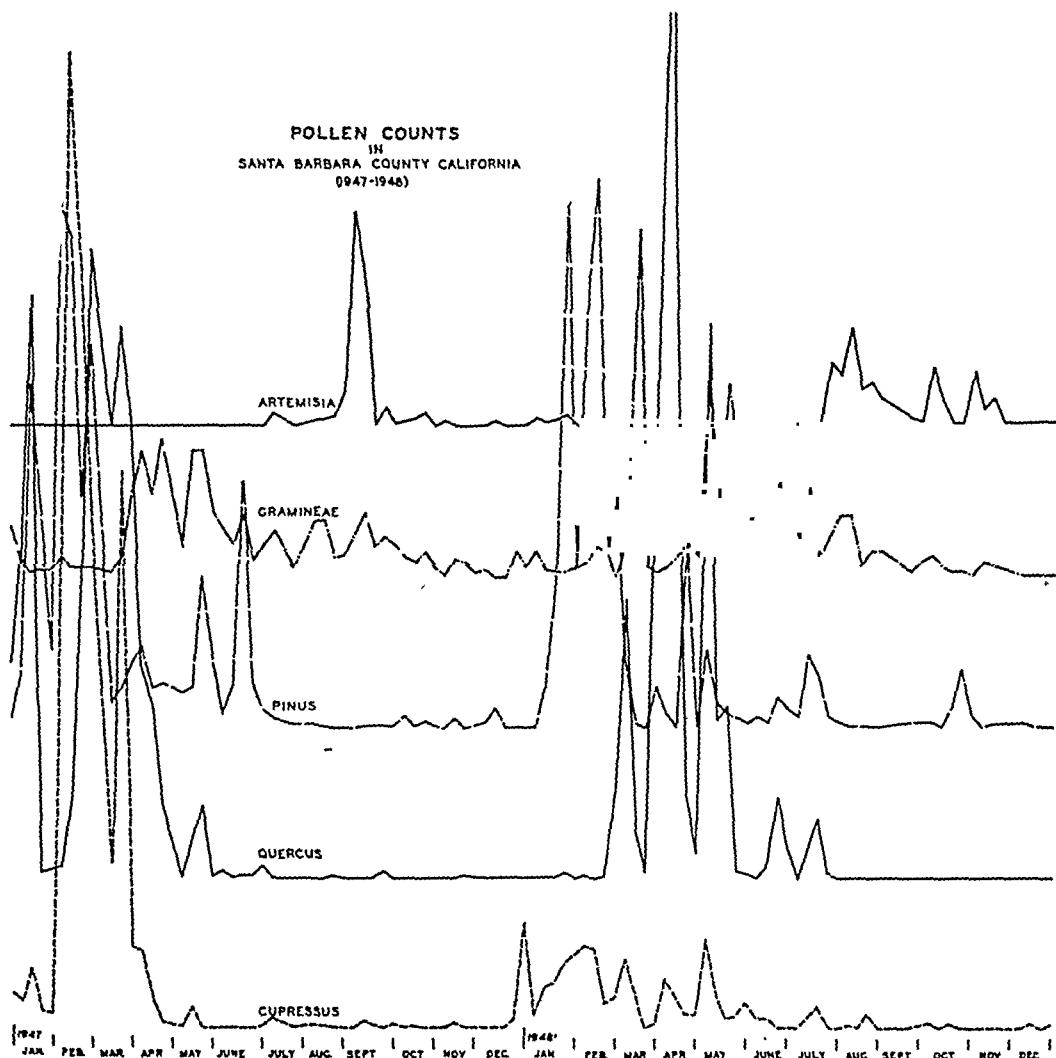


Fig. 1.

TABLE I. POLLEN COUNTS IN SANTA BARBARA, CALIFORNIA

	1947 (entire year)	1948 (entire year)	
1. Quercus	1,675	1. Quercus	1,285
2. Cupressus	1,573	2. Pinus	1,222
3. Pinus	1,263	3. Gramineae	763
4. Gramineae	682	4. Adenostoma	410
5. Schinus	314	5. Cupressus	322
6. Eucalyptus	261	6. Olea	301
7. Artemisia	181	7. Artemisia	200
8. Alnus	118	8. Cocos	155
9. Juglans	116	9. Eucalyptus	143
10. Cocos	96	10. Chenopodium	104
11. Acacia	88	11. Juglans	71
12. Compositae	51	12. Alnus	70
13. Populus	36	13. Populus	68
14. Ambrosia	35	14. Acacia	21
15. Olea	29	15. Ambrosia	13
16. Chenopodium	24	16. Compositae	11
17. Adenostoma	19	17. Schinus	2
18. Ligustrum	3	Unknown	153
Unknown	140		

the actual pollen count with the known growth standing in the county, but this obvious lack of pollen brought this question to our attention. The other outstanding fall pollen found in the surveys south of here, *Artemisia*, is

AIR-CONTAMINANT SURVEY—BURTNES AND ALLEN

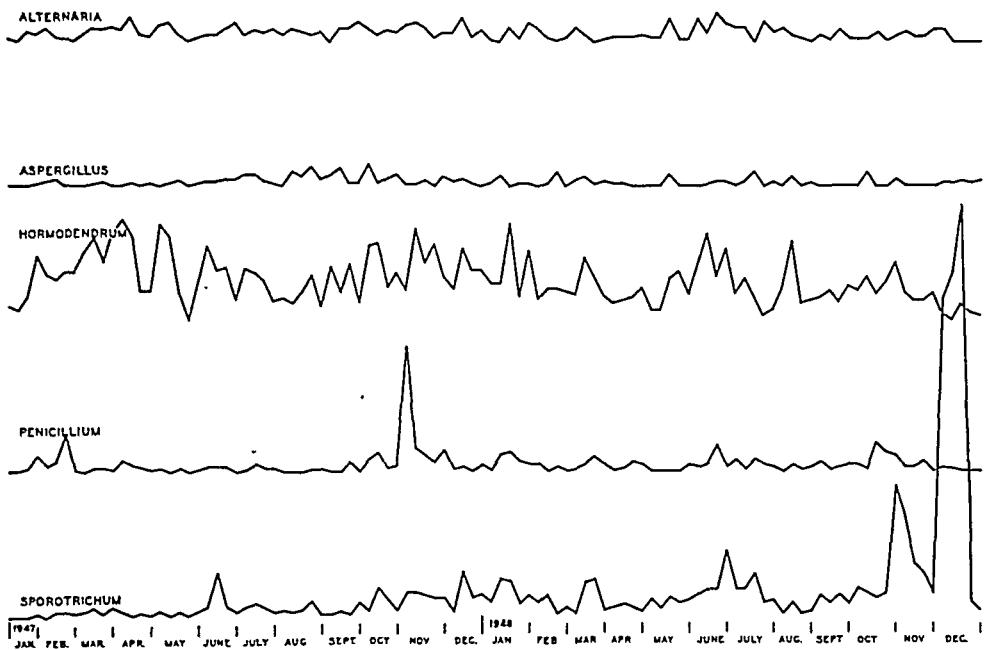
FUNGUS COLONY COUNTS (PLATE METHOD)
SANTA BARBARA COUNTY CALIFORNIA
(1947-1948)

Fig. 2.

TABLE II. FUNGUS COLONY COUNTS IN SANTA BARBARA, CALIFORNIA
(Plate Method)

	1947 (entire year)	1948 (entire year)	
1. Hormodendrum	1,225	1. Hormodendrum	891
2. Alternaria	217	2. Sporotrichum	890
3. Penicillium	200	3. Alternaria	173
4. Sporotrichum	183	4. Penicillium	142
5. Aspergillus	107	5. Epicoccum	85
6. Epicoccum	68	6. Stemphyllium	68
7. Stemphyllium	67	7. Aspergillus	67
8. Macrosporium	51	8. Macrosporium	50
9. Botrytis	29	9. Botrytis	28
10. Chaetomium	13	10. Helminthosporium	18
11. Pleospora	10	11. Mucor	7
12. Mucor	9	12. Pleospora	6
13. Helminthosporium	9	13. Rhizopus	4
14. Rhizopus	5	14. Chaetomium	0
Unknown	312	Unknown	294

TABLE III. FUNGUS SPORE COUNTS IN SANTA BARBARA, CALIFORNIA
(Slide Method)

	1947 (entire year)	1948 (entire year)	
1. Alternaria	765	1. Alternaria	495
2. Rusts	444	2. Rusts	453
3. Stemphyllium	273	3. Macrosporium	185
4. Smuts	166	4. Stemphyllium	128
5. Macrosporium	156	5. Smuts	114
6. Hormodendrum	144	6. Helminthosporium	81
7. Helminthosporium	61	7. Hormodendrum	75
Unknown	76	Unknown	97

also lower than would be expected. In the light of the fact that this study was made in two of the driest years that this county has ever known, it will be interesting to see the count that is obtained in more normal years, especially in these two genera: Ambrosia and Artemisia.

The most commonly occurring pollens found here are shown in Table I. As can be seen, *Quercus* and *Pinus* are so abundant as to warrant comparison with other genera found in large amounts elsewhere. *Quercus* is found to be two and one-half times as abundant as *Gramineae*, even though *Gramineae* is found in nearly every month of the year, while the bulk of the *Quercus* pollen was found in the first four months of the year.

The findings in the study of the fungi follow that of other surveys more nearly in that *Hormodendrum* colonies outnumber those of other groups rather markedly, as shown in Table II and Table III. The *Alternaria* group is second in frequency, and if all its member counts are combined, we still find that there were four times as many *Hormodendrum* as *Alternaria* group colonies in 1947 and three times as many in 1948. The *Alternaria* group count, however, was rather consistent over the two-year period, while the *Hormodendrum* count was 30 per cent more the first year than in the second year. On the other hand, the *Sporotrichum* count was much higher here than elsewhere. This count was much higher during 1948 than in 1947, more than one-third of this figure being found in a three-day splatter of colonies during a three-week period.

Alternaria is more prevalent here than in the San Francisco study by Deamer in 1947, and *Rhizopus* and *Penicillium* show much less importance than found by Schonwald in Seattle. *Penicillium* is well represented here, however, though the count is not as high as found at the beaches in San Diego County.

The accompanying tables and graphs show the frequency and distribution of occurrence of both pollen and fungus spore counts. It will be noted that an abundance of Rust spores is shown on the slide counts and these are often correlated with the increased showing of grass pollen.

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317 West Pueblo Street,
Santa Barbara, California

SEVERE SERUM-SICKNESS TYPE OF PENICILLIN REACTION

Failure of Antihistaminic Therapy

BERNARD M. ZUSSMAN, M.D., F.A.C.A.

Memphis, Tennessee

THIS PAPER is being written, not to add another case report to the voluminous literature about this subject, but to pause for a moment in our mad rush to sensitize an entire population, ourselves included. Since 1943, the literature has abounded with new and interesting forms of penicillin sensitivities, and, with the introduction of the antihistaminic drugs, we all heaved a sigh of relief at the relative ease with which these reactions could be controlled. However, there is an accumulating literature on reactive cases of an unusually severe nature, resisting every kind of antihistaminic drug, and the following is reported as one of this type.

CASE REPORT

The patient, a 34-year-old physician, had been given three injections of 300,000 units of procaine penicillin G in oil (Duracillin) for the treatment of a minor hand injury. Approximately ten days later, he broke out with giant urticaria which rapidly extended over his entire body, including the scalp. His face and eyes were swollen, and the itching was intense. He was given 0.3 cc epinephrine, which was repeated at intervals of two to three hours, and was started on Benadryl 50 mg every four hours and nembutal grains 3. The following day, as the patient's condition appeared worse, he was started on Hydrillin 100 mg and advised to use a 2 per cent Pyribenzamine ointment (Ciba). In addition to the generalized urticaria and edema, there were severe headache, polyarthralgia and slight neck rigidity. The patient appeared very ill, temperature 102° and pulse 120. A curious phenomenon noted was that when patient lowered his legs over the side of bed, they became painful and white. This was attributed to interference with the circulation to the legs caused by pressure on the arteries by the edematous reaction, resulting in local ischemia. As the two previous antihistaminic drugs appeared of no avail, a third, Pyribenzamine 100 mg. every four hours, was tried. In addition he was given 50 mg nicotinic acid dissolved in 10 cc distilled water intravenously, which appeared to afford temporary relief. That night the patient's condition appeared even worse, and it was necessary to resort to morphine sulfate $\frac{1}{4}$ gr to give some fitful relief.

Starch baths, 50 per cent glucose intravenously and a fourth antihistaminic, Neo-antergan 100 mg was tried. By now the patient had been ill for five days and it was felt that the allergic reaction might subside spontaneously by this time.

After three or four doses of Neo-antergan, the patient stated that he felt much better, and his urticaria appeared to be diminishing. Whether or not this was coincidental with a spontaneous remission of the allergic reaction is conjectural. At any rate by the next (sixth) day his rash was completely gone and he was discharged.

DISCUSSION

The number of cases in which the antihistaminic agents do not have any effect are rarely reported. Following is a brief survey of the recent litera-

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PENICILLIN REACTION—ZUSSMAN

ture showing the failure of drug therapy in penicillin reactions of the serum sickness type. Davis⁴ reported two cases of severe urticarial delayed reactions following intramuscular penicillin in which no appreciable benefit was obtained from Benadryl or from the sympathomimetic drugs. He also states that he has seen eight moderately severe urticarial reactions following oral administration in which Benadryl, et cetera, failed to relieve the symptoms in two of the delayed serum sickness types. One of his cases had urticaria and pruritus for twenty-eight days despite all therapy before the symptoms finally subsided. Friedlaender⁶ reported a case of urticaria, polyarthritis, and severe generalized edema following penicillin, in which Benadryl was unable to control the polyarthritis but did benefit the other symptoms. He suggested that histamine might play a greater rôle in urticaria than in other allergic manifestations, because it responded more readily to the antihistaminic drugs. Kendig and Toone⁸ report three cases of delayed serum sickness type of reaction following penicillin. In one case, Benadryl gave little relief from symptoms due to the urticaria which lasted for two weeks. Two of their cases had previously received penicillin, and these authors felt that subsequent courses of penicillin therapy increase the hazards of sensitization. Watson¹¹ reports a case of delayed serum sickness type of reaction on the ninth day following 250,000 units of aqueous penicillin for three successive days. This patient had severe pruritus and urticaria which was not relieved by Benadryl or epinephrine in full therapeutic dosage and which lasted for seven days. Wilcox reports a case of urticaria following penicillin therapy in which the concomitant use of Benadryl and epinephrine caused collapse and both drugs had to be discontinued.

That the method of administration has nothing to do with the allergic reactions to penicillin has been shown by the work of Barach,¹ who used penicillin aerosol in ninety-one courses of penicillin therapy in sixty asthmatic patients (some of this may have been given systemically): "Reactions to penicillin necessitating interruption of therapy occurred during twenty-four of the ninety-one courses. Exacerbation of asthma was seen in fifteen patients, urticaria in ten, reddened tongue in seven, and fever and swollen joints in one." Gordon⁷ reported three cases of delayed serum-sickness reactions to penicillin therapy, two of which had penicillin previously. He stated that the disease ran a self-limited course of seven to ten days, regardless of the type of therapy employed. Brown² states that, in his personal experience with urticaria and angioneurotic edema following procaine penicillin G in peanut oil, no alleviation of symptoms occurred following 500 and 100 mg doses of Pyribenzamine, Thephorin, Thenylene, Neohetramine, or Decapryn, with mild alleviation following ingestion of Trimeton. He states that Demerol in 50 to 100 mg doses controlled the associated pruritus, but had no effect on the urticaria or edema.

That delayed type of serum-sickness reactions may end fatally is seen in the case reported by Wilensky,¹² whose patient had received 720,000 units of penicillin following resection for gastric carcinoma. On the sixth post-operative day, he developed vomiting, fever of 104° and a scarlatiniform rash which became urticarial on the following day. Despite immediate cessation of penicillin and substitution of sulfadiazine, the patient's condition rapidly deteriorated and he died. No mention of antihistaminic therapy was made, and the mechanism of the patient's death was explained on the basis of delayed anaphylactic shock as reported. Since then, several other fatalities have been reported following penicillin therapy: in one,

as a result of acute edema of larynx and in the other, as a result of acute anaphylactic shock following an injection of penicillin which was thought to have entered a vein, as reported by G. L. Waldrott.¹⁰

CLASSIFICATION OF SERUM-SICKNESS REACTIONS

1. The *delayed serum-sickness type of response* usually follows within seven to ten days after the primary injection, though delayed responses as long as thirty to forty-five days have been reported.

2. *Accelerated serum sickness* occurs after a much shortened interval, from several hours to several days. This type of response generally follows a second injection of serum whether or not the primary injection was followed by clinical manifestations of serum sickness. The symptoms of the accelerated type resemble those of ordinary serum sickness but are likely to be more violent.

3. *Local serum sickness:* In some cases there is no generalized reaction but merely local swelling and tenderness at the site of injection. In other cases, the local reaction precedes the general eruption by one or more days.

PATHOGENESIS OF SERUM-SICKNESS TYPE OF PENICILLIN REACTION

The term serum sickness or serum disease was originally applied by Von Pirquet to the familiar sequellae which followed by a number of days an injection of foreign serum. Horse serum is the most common serum used, although serum from other animals (hogs, sheep, rabbit, et cetera) can and do produce serum sickness. However, since the turn of the century, the use of parenterally administered extracts has been accompanied by a markedly increased incidence of allergic reactions. Injectable vitamin products, sclerosing fluids, organic extracts (liver, insulin, glandular preparations, vaccines, toxoids, drugs, and antibiotics) constitute a formidable group of materials to which the patient can become sensitive. The development of antibiotics and chemotherapeutic drugs has been a two-edged sword. "It is well, however, in this connection, to remember that sensitivity to the chemicals may become increasingly important as their use increases and opportunity is given for sensitization to them to develop."¹³

That severe irreversible tissue destruction may follow serum sickness has been proven by the epic work of Rich and Gregory⁵ in which they demonstrated the typical lesions of periarteritis nodosa in patients who died following serum sickness or allergic reactions to sulfonamides. Furthermore, they were able to reproduce these same lesions in experimental animals following single and repeated doses of foreign serum to cause serum sickness. Recently, the sensitizing properties of penicillin have been studied by McClosky and Smith,⁹ who demonstrated anaphylactic sensitization in guinea pigs with repeated small doses of commercial penicillin.

CONCLUSION

- Penicillin given by oral ingestion, topical application, aerosol inhalation, or by injection sensitize a certain per cent of the population.
- Allergic reactions occur most frequently in patients who have had several courses of penicillin and the incidence is definitely on the increase.
- The antihistaminic drugs frequently are unsuccessful in controlling these penicillin reactions, especially the more severe ones.
- Skin tests are unreliable in predicting the occurrence of reactions which may be fatal.

(Continued on Page 771)

MARITAL ADJUSTMENTS IN THE PARENTS OF ALLERGIC CHILDREN

HYMAN MILLER, M.D., F.A.C.A., and DOROTHY W. BARUCH, Ph.D.

Beverly Hills, California

THE PRESENT paper reports on one phase of a continuing study of the psychosomatic aspects of allergy which has shown the emergence of a characteristic dynamic pattern in allergic individuals. Of primary importance in this pattern is the emotional interaction between mother and child.

Generally, it is the mother who determines the emotional climate in which any child finds himself. The child's dynamic pattern varies with this climate. His wholesome development depends on the presence of maternal love. But, as pointed out by many observers, maternal love is not always forthcoming. Some children are raised in a climate of maternal rejection.^{8,12,13}

Resentment is every child's normal and healthy reaction to insufficient love from his mother. This resentment can be expressed outwardly, or its outward expression can be held in and blocked. In any case, it creates psychic energy which must be discharged. The nonallergic child characteristically discharges resentment which he feels against his parents by bringing it out quite directly against his parents in manifest misbehavior that annoys or aggravates them. On the other hand, the allergic child characteristically is unable to bring resentment out as directly. In him there is a block to such frankness. The hostility he feels against his parents is repressed. But the psychic energy of the hostility must be discharged. This he tries to accomplish through physical symptoms. The physical symptoms are used then to express, in masked fashion, the hostility generated by the need for more love. They also cry for more love.⁴

The allergic child is hungry for love and he is inordinately full of anxiety. He fantasies and fears losing his mother. As shown in another study, the first onset of his symptoms often follows traumatic episodes which to him stand for the loss of his mother.⁹ In these children, the fear of such loss then seems to arise from the experience of maternal rejection.

A high proportion of allergic children live in a climate of maternal rejection. The climate may be set even prior to the child's birth.¹¹ Our sample now contains one hundred allergic children studied physically and psychologically.¹⁰ Of the one hundred children, ninety-seven were rejected (97 per cent). Only three were not.

In a control group of sixty nonallergic children similarly studied, twenty-two children were rejected (36.7 per cent). In comparison with the allergic group, this gives a highly significant critical ratio of 9:4, indicating that the chances for the allergic child's being found in the climate of maternal rejection is far greater than for the nonallergic child.

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Maternal rejection of the allergic child is a basic element in the onset, persistence, and curability of his symptoms. In consequence it is essential not only to recognize the rejection, but also to accept the rejecting mother as sympathetically as the rejected child. Abhorrent as our culture and our own culturally induced attitude make it seem, maternal rejection has its own precursors just as any illness has its precursors. Therefore, it becomes not only important but useful to gain whatever insight we can into the etiology of maternal rejection.

A rejecting attitude toward a child is not an isolated phenomenon in the maternal personality. It is only one manifestation of a complex emotional pattern. Diverse manifestations of the pattern may be exhibited in relationships with other members of the family and with the outside world.

Studies have indicated that a rejecting attitude toward the children goes hand in hand with a poor marriage relationship.^{3,5,6,12,13} The marriage relationship, in turn, has been found to be influenced by sexual adjustment.^{2,7} Dickinson, for instance, says, "Complete unity in marriage depends on sexual unity." He states that discord over relatives, money, work, management of the children and the home are secondary to sexual conflict. He relates satisfactory sexual adjustment to the achievement of orgasm by both partners.

Since sexual maladjustment is the same entity whether it appears in the family of an allergic child or in the family of a nonallergic child, the data on sexual relationships in the two groups were combined. In our study, we had information on sexual adjustment in 141 cases.

Also, since rejection is the same entity whether it appears in the mother of an allergic child or in the mother of a nonallergic child, for purposes of the present paper the rejecting mothers in both groups were combined. There were evidences of rejecting attitudes in 119 mothers.

Sexual maladjustment was expressed in dissatisfaction concerning such items as the partner's impotence, premature ejaculation, demands for too frequent intercourse, a lack of interest and too infrequent demands, or demands for what the woman termed "unnatural sex practices." But in far greater number, sexual maladjustment was admitted in terms of the woman's own dislike of intercourse accompanied by lack of orgasm.

On this basis, in the 141 cases, 103 women admitted to sexual maladjustment; thirty-eight (27 per cent) claimed they were well adjusted.

Of the 103 women in the maladjusted group, eighty-seven (84 per cent) were rejecting mothers. Sixteen (16 per cent) were not rejecting. The highly significant critical ratio of 13.7 indicates that where sexual maladjustment was present, there was a significantly higher incidence of maternal rejection.

Of the 119 rejecting mothers, information regarding sexual adjustment was available on 101. Of these, eighty-seven (86 per cent) admitted to sexual maladjustment; fourteen (14 per cent) claimed they were well

adjusted. The highly significant critical ratio of 14:7 indicates that among rejecting mothers there is a significantly higher degree of sexual maladjustment than among nonrejecting mothers.

But the marriage is not the only precursor to be considered. Studies such as those by Despres,¹ Figge,³ Newell,^{12,13} Stein,¹⁴ Symonds¹⁵ and Wolberg¹⁶ have shown that the marriage does play a part in the formation of the rejecting attitude. But so also do the mother's own childhood experiences play a part.

In our patients this was confirmed.

The following cases illustrate, in brief, how the mother's childhood influences her marriage, her attitude toward her children, and even her husband's relationship with the children.

Mrs. D. was a woman in her early thirties. In spite of an outwardly quiet maternal concern, she conveyed a feeling of inner desperation and apologetic resentfulness. Her two-year-old boy had recently developed asthma. Of him she said, "He drives me crazy. He wears me out. Life hasn't been easy since I've had him. I'd never have had him if I'd known."

In her own life she had been and still was greatly dependent on her mother. Whenever her child got sick, she called her mother before calling the doctor. She frequently left the child in her mother's care during the day. When she first came into group therapy, she could only express appreciation of her mother's helpfulness. Later, she betrayed glimpses of deep feelings of resentment toward her mother, who she felt had never really cared about her. Of these feelings, she was greatly ashamed. She would repeatedly retract and cover them over with renewed praise.

In contrast, she "worshipped" her father. His last illness had occurred during her pregnancy with the patient. In spite of her pregnancy she took over his care, lifting his paralyzed body and attending to his physical needs. "He wanted me, not my mother, because I was his favorite," she explained. "Being pregnant made it terribly hard. But I managed all the same."

In her marriage, she had quite apparently sought to find another father. She had married a divorced man eighteen years her senior. "He reminded me so much of my father," she said. Sexual adjustment was poor and she never attained orgasm. Unconscious oedipal feelings were apparently too much in the way. In an attempt to resolve the inner conflict, she renounced sexual contact on religious grounds.

She felt so "nervous," however, that she continuously tried to get her husband to take over the child's care during evenings and nights when he was ill. In passive, escapist fashion, the husband evaded this responsibility, drinking to excess and staying away from home.

Thus the child got neither the mother's love nor the father's. In his asthmatic attacks, he constantly cried to be held.

* * *

Mrs. S., a woman of twenty-four, characteristically covered her feelings with an air of flippancy. However, when she spoke of her three-year-old allergic girl, she suddenly gave way to a strong onrush of feeling. "I actually felt I could kill her," she said. "I wanted to throw her against the wall and bash her brains out."

Her own mother had died in Mrs. S.'s adolescence. Her death made it especially difficult for Mrs. S. to admit the ambivalence toward her which gradually came out in the therapy group. She would say of her mother, "She really never loved

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me. She would punish me terribly. She'd tell me all the time not to be bad. I was afraid to do anything. But—she really was good to me."

With her father, she recalled some intimate scenes. She recounted, with excited embarrassment, that after her mother died, she had shown herself off to him in her slip and he had fondled her breasts.

When her father remarried, she resented her stepmother and ran away to the home of the man whom she subsequently married. Obviously putting him in her father's place, she sought to have him take care of her. As he said in an interview, "I've been a father to her. I've had a rough time being a boy friend and a father both."

Their sexual adjustment was poor. She never experienced orgasm.

In the therapy group which she entered, the death wishes she had expressed in the beginning toward her child were ultimately related to her death wishes to her mother. Just as she had earlier tried to prove herself a loving daughter, she had later tried to prove herself a loving mother.

In spite of rejecting her child, she would not let her husband have anything to do with the child's care. When he demanded that he had a right to take part in it, she would pack up and leave, taking the child along, only to return when the care grew too burdensome.

In this unstable environment, the child could gain adequate love from neither and felt lost and insecure.

* * *

When Mrs. G. first entered therapy with her asthmatic boy of seven, she, too, was dependent on her mother, turning to her continuously for help and advice. Bit by bit, with great guilt apparent, she brought her deeper feelings out. She gave a picture of her mother as too busy, too burdened, having failed to take time even to gather the family around the dinner table. Mrs. G. recalled herself as a child, standing at the kitchen sink, eating alone, feeling shut off and rejected.

In her early years her father had had a psychotic episode. This had been preceded by frank sex play with his daughter which she enjoyed until it ended in an attempt at rape.

In her marriage she found it difficult to achieve complete sexual adjustment. She had chosen a husband whose quiet, contained personality gave promise of the dependability she had always craved from her father. Actually her husband was quite immature. This left her disappointed and with greater responsibility than she felt able to shoulder. She swung back and forth between attempts to do more than her share for the child and attempts to get her husband to take over. Fundamentally, however, she rejected her child. In her therapy she came upon a fantasy that had hitherto lain unconscious—in her own words, that her child "was the product of an incestuous union" with her own father. The pressure of this in her unconscious had created such a guilt that it had contributed to the rejection of her child. Even so she managed to cover the rejection with the same excessive devotion she had used in covering her earlier animosity to her mother.

Again in this case, the child felt a lack of both maternal and paternal emotional support.

* * *

Mrs. A., the mother of a twelve-year-old asthmatic daughter, herself had a mother whom she felt was conscientious but without spontaneous good humor or warmth. Even so, Mrs. A. had pinned a picture of a devoted mother over her inner picture of the rejecting mother whom she resented.

With her father Mrs. A. had "more in common." "He was a good man, upright and moral," she stated with pride. She married a man the essence of uprightness and morality, over fifteen years older than herself. Their sexual adjustment was poor.

Mrs. A. progressively turned more and more of her daughter's care over to her

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husband. He met this responsibility by making great demands for perfectionistic achievement which the girl could not meet. Mrs. A. finally ended by divorcing her husband and leaving the child under his repressive domination.

* * *

Mrs. F., the mother of two allergic girls with asthma and eczema, met life with starry-eyed romantic unrealism. Her father and mother had separated when she was small and she had not seen her father again until her late adolescence. Her mother had alternately deposited her with her maternal grandmother or had taken her traveling with a governess in immediate charge. Only after several months of individual therapy did Mrs. F. glimpse the "murderous" impulses toward her mother which lay behind her fawning façade.

Her father she remembered as a prince charming, "full of fun." When she was in her teens her mother remarried and she turned with passionate devotion to the stepfather, looking to him for the steadiness, stability and love she had missed.

In her own marriage, she sought to recapture the prince charming of her childhood. Her husband was "glamorous, tall and handsome. Full of fun."

Sex, she said, was not important. "I'm not very much that way. I really care more about affection than about sex."

Her children were unanticipated and unwelcome. The fairy prince turned out to be a play-boy. He failed to take responsibility and the marriage ended in divorce. Mrs. F. then packed up and removed the children altogether from contact with their father, traveling to a distant city to live near her stepfather on whom in spite of his disdain she continued to lean for guidance and advice.

Again her children had neither father nor mother on whom they could rely to meet their emotional needs.

From these and other cases several repetitive themes appeared which suggest a pattern in the lives of these rejecting mothers which will bear further investigation.

1. In their childhood these mothers felt deprived of their own mother's affection. They unconsciously betrayed that they felt rejected.

2. Resentment to their mothers appeared to be more intense and more deeply repressed than in women who were not rejecting. By the same token, they were apprehensive about going counter to their mothers' wishes. They showed more marked dependency and maintained more obedient devotion.

3. They fled from the awareness of their hostility to their mothers. In therapy, with the slightest dawning of such awareness, they were prone to retract quickly and once more to cover over.

4. They reenacted their relationship with their mothers in their relationship with their children. Instead of the child's being a person to whom they owed devotion, the child became a person who made demands.

5. The hostility felt to their mothers was duplicated in the hostility felt to their children. So great was the resultant pressure that in general they found it harder than other mothers to brook any expression of hostility from the child lest it act as a trigger to their own pent-up store.

6. To avoid the danger of losing control of themselves, they curbed their children's hostility by excessive restrictions, care and demands.

7. There were marked unresolved oedipal feelings in these mothers which

earlier had augmented the animosity toward their mothers and later had influenced their choice of a husband.

8. In several cases (as in Mrs. G's.) material brought out by the mother suggested that the child had unconsciously been fantasized as the child of the mother's father. The ensuing guilt then had brought further impulsion for the mother to deny her child.

9. The sexual adjustment of these women was ordinarily poor with orgasm usually lacking or sex drive inadequate and low.

Basically, these women were deprived, insecure individuals evidencing an unreadiness and inability to assume a mature sexual and maternal rôle. The rejecting mother comes with her own childhood experiences into her marriage. Her marriage, in turn, may either activate or aggravate conflicts which were born in the past. In its turn, marriage may bring experiences which are unbearable either of themselves or because of her set from the past. These may add to her own feeling of insecurity. Both present and past color her feelings toward her husband. They color her feelings toward her children. Subtly, or otherwise, they influence the relationship which her husband has with the children and the child's conflicts out of which his somatic symptoms may arise.

In our sample, in general, the interaction between husband and wife and its influence on the father-child relationship seemed to fall into four patterns:

1. The mother, because of her desire to avoid a mother rôle, made demands that the father take over the responsibility of the child. He either acceded with resentment or he escaped into immersion in work, drinking, and the like.

2. The mother, because of her unconscious drive to prove herself a good mother to cover her inner rejection, pushed the father away from the children. This ended either in conflict or in the father's acceding.

3. The mother chose a husband so immature in his own development that he failed to assume a father rôle. This left the mother holding unwelcome responsibility added to at times by casting the father in the rôle of another burdensome child.

4. In a few cases, the father assumed an oversolicitous rôle, attempting to make up for his wife's failure, which he unconsciously resented but did not wish to admit. This, the child felt, and, as a result, the father also failed in furnishing the emotional security which the child should have had.

In conclusion, it may be said that a mother's rejecting attitude is a product of many factors for which she is no more responsible than the allergic child is responsible for his clinical symptoms. Her suffering is as real as her child's. Our cultural standards cause her attitude to be as repugnant to herself as it is to the society which sets the standards for her. Our culture condemns her for an attitude which is of its own making. As one understands the factors that enter into a mother's rejecting attitude,

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it becomes possible to treat both mother and child with greater sympathy and skill.

SUMMARY

1. In this, as in previous studies, maternal rejection is seen as an important item in the emotional climate of the allergic child's environment.
2. In its etiology, maternal rejection is found to be related to the mother's emotional immaturity, a product of her own life history.
3. Of primary importance are the mother's rejection by her own mother, the unresolved oedipal attachment to her father, and the hostility to her mother derived from both.
4. As a result of childhood conflict, sexual adjustment in the marriage of these women is poor.
5. Statistically, poor sexual adjustment is significantly related to maternal rejection.
6. The influence on father-child relationship is discussed.

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MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

XIV. Fungi in Aerobiological Populations. The Fungus Flora of *Tillandsia* Species (Ball and Spanish Moss)

MARIE BETZNER MORROW, Ph.D., and EDNA CRONQUIST WHEELER, M.A.
Austin, Texas

PHENOMENAL interest in the subject of fungi in relation to inhalant allergy has developed in the last twenty-five years. Since 1925, when Van Leeuwen proposed that air-borne mold spores were a cause of inhalant allergy in Holland, an increasing number of workers here and abroad have contributed to our present knowledge concerning the allergenicity of molds and other fungi. During this time an increasing interest has been indicated in the possibility that the so-called "epiphytic mosses," which are not mosses at all, but members of the pineapple family (Bromeliaceae), as represented by "ball moss" (*Tillandsia recurvata* Linn.) and "Spanish moss" (*Tillandsia usneoides* Linn.), may bear some relation to the incidence of inhalant respiratory allergy. This is particularly true in those sections of the southern United States and elsewhere where these species are found in more or less profusion. In this paper the word "moss" will be used for these epiphytic bromeliads, and the phrase "ball moss" and "Spanish moss," for *Tillandsia recurvata* and *Tillandsia usneoides*, respectively.

Some studies have been reported on these mosses with respect to their allergenic properties, but nothing was done with the fungi, nor were they mentioned as contributing factors. Fifty patients in Florida³ were tested for sensitivity to the pollen and to the ground fiber of the plant, with negative results in both cases. On the other hand, positive results were reported in New York² with the extracts of new, unused Spanish moss as employed in furniture upholstering, and also with the ground new moss insufflated into the patient's nostril. It was implied that this sensitivity was due to the moss material itself, but it could be explained by fungi or other extraneous substances present, since the moss material was not sterilized. New material was used in order to reduce the possibility of contamination, where contamination connotes anything that might get into the material during use, and without considering the possibility of fungi and other extraneous substances that might be associated with the new, unused moss material.

It has been apparent for some time to physicians, mycologists, plant pathologists, and others, whose interests extend into this field, that detailed studies of these bromeliads as potential hazards for sensitive individuals from the standpoint of the fungi present was desirable, and

From The University of Texas.

Dr. Morrow is an Honorary Fellow of The American College of Allergists.
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1950, St. Louis, Mo.

would be forthcoming. The fact that both ball and Spanish moss are found in and around Austin, Texas, was a determining factor in undertaking the present investigation at The University of Texas. Also, an exploratory study of these had been made earlier (Lowe and Morrow, 1939).

The present studies were planned for the purpose of finding out what relations, if any, exist between the presence of ball and Spanish moss plants in a given location or environment, and the air population at that location; and whether the presence of these two plants in a given location indicates a potential source of allergenic material in the air population there; and whether these plants, by implication, therefore constitute a potential hazard with respect to inhalant respiratory diseases, and as such, should be investigated in analyzing an environment for sensitive individuals. Three objectives were apparent. One was to determine what fungi, if any, are present on ball and Spanish moss in a natural habitat. A second was to determine, in so far as possible, whether the fungi present on the living plants are a part of the fungus population found generally in that environment, that is, on other substrates, or whether these are confined to the moss plants, and thereby constitute a moss flora. Finally, a third objective was to determine whether the fungi on the respective moss plants are generally air-borne, as indicated by their presence on adhesive slides and culture plates exposed in the same environment.

Ball moss (*T. recurvata*) which grows in gray-green spherical tufts on some twenty-five tree species from Florida to Argentina and Chile, and the hoary-gray Spanish moss (*T. usneoides*) which hangs in pendulous festoons from a number of trees extending into tropical America and southward into Brazil, are among the most characteristic plants of our southern regions.

The *Tillandsia* mosses, which are always epiphytic, and never parasitic or saprophytic, are perennial herbs with no roots, but absorb moisture through the tiny scales that cover the leaves and stems. The necessary minerals are present in the rain and in the dust from the air which collect in and among the scales of the plants. It was taken more or less for granted that these scaly surfaces were also substrates for fungus spores and mycelial fragments. As a matter of fact, fungus pathogens and other organisms associated with *Tillandsia* species have been described (*Psilonia cylindrospora*, *Volutella cylindrospora* and *Colletotrichum bromeliae-carum*).⁵ Without rushing the discussion of the results, it might be said here that none of these was encountered in the present studies.

Although it has been reported that Spanish moss is found mostly on lowland timber, and ball moss on upland timber,¹ these two species are found commonly on cedar elm (*Ulmus crassifolia* Nutt.) in the Austin region; in fact, the two are frequently found on the same tree. For this reason, cedar elm was selected as the tree source of both mosses in these experiments. Parasites on cedar elm have also been listed (*Cylindro-*

sporium tenuisporium, *Gleosporium ulmeum*, *Gnomia usnea* and *Urnula geaster*).⁵ These, likewise, were not recovered.

Ball moss and Spanish moss, together with the cedar elm, were studied as the living substrates. In order to determine whether the fungi isolated from the living plants are specific for these sources, or whether similar fungi might also be found on other substrates in the same environment, other surfaces were examined: namely, sterile ball moss, sterile Spanish moss, sterile filter paper, and sterile cheese cloth. These were placed in the same environment with the living moss plants for a period of ten to twenty days before examination. In the results, the living plants are designated as "normal," the other materials as "sterile."

At the same time that the living substrates and the corresponding other materials were sampled, air exposures were made in the same environment, so as to determine whether the fungi isolated from the different surfaces were also air-borne.

Dilution and direct plating were employed for the study of the substrates, and agar plates were exposed to sample the air population for air-borne fungi. The direct method included direct plating of portions of the substrates unwashed (unW) and washed (W), and the corresponding washings (Wg).

The agar plates were exposed for two-minute intervals. The number of fungi isolated from a two-minute exposure plate, when multiplied by the factor 21,⁴ gives a figure comparable to a twenty-four-hour pollen count which is standard in aerobiological analysis.

Three experiments were designed so as to compare the same location at different dates, and to compare different locations within the city. Experiment 1. West 22nd Street; beginning February 29, 1944; sampled March 11. Experiment 2. West 22nd Street; beginning April 4, 1944; sampled April 17. Experiment 3. Windsor Road; beginning April 10, 1944; sampled April 29.

The results presented in this paper consist of the outstanding facts revealed in the studies which lend themselves to a short paper, and are presented in summary form. Details of method, qualitative and quantitative tables, lists, figures, graphs, photographs, and other details, while invaluable for a record, are omitted here, as well as the historic aspects. For the task of collecting and recording a voluminous amount of data, special credit is due the junior author.

Some sixty-five different species of fungi were isolated. About fifty species were isolated from plant material; of these, thirty-five were recovered from living substrates. Thirty-one species were recovered from living mosses, twenty-five from ball moss, sixteen from Spanish moss, and seventeen from cedar elm.

Seven species were isolated only from living substrates; five from mosses, four from ball (*Helminthosporium* sp. No. 46, sterile pale species No. 50 and No. 52, and an undetermined sclerotial-like species No. 40),

and one from Spanish moss (a sterile pale species No. 39); and two from cedar elm (*Phoma* sp. No. 84 and an undetermined pycnidial species No. 71).

The pathogens listed by Seymour (1929)⁵ and mentioned by Birge (1911)¹ for mosses as hosts, and those listed by Seymour for cedar elm apparently were not recovered in these experiments. Some of the fungi encountered (*Phoma* sp. No. 84, *Helminthosporium* sp. No. 46, the pycnidial species No. 71, and certain of the other undetermined species), by virtue of being confined to a living substrate, suggest phytopathogens, but they were not indicated as such in this study.

Furthermore, it was not possible to determine whether any of the fungi isolated only from the living mosses were specific to the growing plant. Only one of these (the sterile pale species No. 52) was isolated when plant portions were plated directly. Not any of these were recovered from the washed portions so as to indicate their attachment in some way to the plant tissue.

The dominant fungi included some of the well-known cellulose decomposing genera (*Trichoderma*, *Chaetomium*) which, when present, may very probably be involved in the natural retting process which is the fate sometimes of these mosses. A number of the dominant fungi were recognized as soil inhabitants which are known to be air-borne.

Most of the dominant fungi encountered throughout the experiments were recovered from the living mosses, but they were also recovered from one or more of the other substrates examined, as well as from the air-exposure plates. At least seven species (*Hormodendrum cladosporioides*, *Alternaria tenuis*, *Alternaria humicola*, pale yeasts of the *Saccharomyces* type, *Aspergillus niger*, *Fusarium elegans*, and a pycnidial species No. 42) were recovered from all substrates. Four of these (*H. cladosporioides*, *A. tenuis*, the pale yeasts, and *A. niger*) also appeared on the air-exposure plates. Two of these (*A. niger* and *F. elegans*) were identified with the direct plating; the others appeared more or less consistently in both dilution and direct plates. These cosmopolitan dominants stand out not only because of their universality with respect to substrates, but also because they are found generally in the air populations of the same environments, and, furthermore, because of the high numbers in which they occur when quantitative counts are made.

High counts of the fungi, as well as a relatively large number of species, were identified with the living mosses, but this was particularly striking for the ball moss with the highest total counts (22×10^5) and individual counts of *Hormodendrum cladosporioides* (11×10^5), *Alternaria tenuis* (4×10^5), *Fusarium elegans* (1×10^5), and a *Phoma* species (3.5×10^5). Although the pale yeasts were not included in the total counts, they were recovered from the living ball moss plants in considerably high numbers (17.5×10^5). The occurrence of high counts and a large number of dif-

(Continued on Page 785)

CLINICAL OBSERVATIONS IN THE USE OF COMBINED CALCIUM-ANTIHISTAMINE THERAPY IN THE TREATMENT OF URTICARIA

A Preliminary Report

WILLIAM PARKER, M.D.

St. Louis, Missouri

PRIOR to the widespread use of antihistaminic drugs, intravenous calcium therapy was widely used as a method of treatment for urticaria.³ Experience with this method of treatment varied widely. This may perhaps have been due, at least in part, to the fact that newer treatments for these conditions have constantly appeared in the literature, replacing older treatments and making an investigation less important, especially of late, with the advent of antihistaminic therapy.

In spite of the advance of therapy in this field, the dermatologist is frequently confronted with those cases of urticaria which do not respond even symptomatically to newer methods of treatment, so that he often falls back upon older, discarded methods. Some investigators have recently reported the use of histamine desensitization as a therapy quite contrary to the use of the antihistamine approach.^{5,6,7} It is precisely such a group of cases that is included in this report.

This group constitutes twenty such cases. In all, the history was generally similar. The eruption came on acutely, was not preceded by previous attacks, was associated with nervousness, and responded very mildly or not at all to antihistamine therapy. In all cases, attempts to establish a history of allergy proved fruitless, and patch tests or scratch tests, or both, were non-revealing. The twenty cases chosen were singled out particularly for their resemblance to each other, not only subjectively, but objectively as well. Besides the usual generalized eruption of wheals and the presence of dermatographism, there was also an associated arthralgia, with swelling in one or more joints, most commonly involving the ankles, wrists, and knees in that order.

All of these patients were treated by combined calcium and antihistamine intravenous therapy, supported by oral calcium and antihistamine therapy. In all cases, the patients showed the usual response to calcium therapy immediately after completion of the injection—a sensation of severe heat, starting in the throat, and descending progressively to the feet. This was followed by complete relief from itching for various periods, lasting from one hour to three days, with subsidence of lesions, but without complete disappearance. A noteworthy observation in these cases, not found in previous literature, with a subsequent reaction about two hours after the injection, when the patient would suddenly begin to feel slightly nauseated and would develop aches and pains in the affected joints, as

The calcium used in this work was neo-cagliucon for the intravenous route, and calcibronat effervescent tablets or granules for oral administration. Neo-cagliucon and calcibronat are respectively calcium gluconogalactogluconate and calcium-bromido-galactogluconate, which are double salts and maintain their stability without foreign buffers. Neo-cagliucon was used because of its high solubility. Calcibronat was used to obtain a mild sedative effect.

The antihistamine used was Benadryl, because of its availability for intravenous use as well as the mild sedative effect when given through either the intravenous or oral route.

well as in the muscles, usually in the upper and lower extremities, along with a sensation of "feverishness" or of feeling "hot and cold" all over the body. These symptoms in about half of the patients were associated with a feeling of weakness, necessitating bed rest. In all cases the symptoms subsided in about three hours and were followed by complete relief from swelling and arthralgia. The wheals, although still present, stopped itching. This freedom from pruritus, in most cases, remained for about three days, and nineteen of the patients reported no recurrences of the swelling or arthralgia. One patient had a recurrence of these symptoms after an upper respiratory infection, one month later, which subsided after a day's treatment of the infection with aureomycin.

REMARKS

Attention is directed to the similarity in response to this treatment by the above-mentioned cases, with the response one obtains with histamine desensitization therapy when the flushing dose is reached, and is followed by similar symptoms. The possible explanation of the above recognized phenomenon may lie in the following: excess histamine has a toxic effect on cell membranes, increasing their permeability and transudation with the clinical manifestations which follow. The antihistaminic agents, by counteracting the histamine, help to allay the phenomenon temporarily. The calcium, by playing a part in normalizing tissue permeability^{2,1,1} further helps to allay this phenomenon; hence, this probably accounts for the synergistic effects of the combined therapy. The biochemical and physical functions of calcium, in their relationship to the histamine antihistamine phenomenon, are in need of further investigation, and such investigation may lead to considerable improvement of antihistamine therapy in providing a lead to maintaining permanency of the effects from antihistamine therapy, heretofore lacking.

CONCLUSIONS

1. A preliminary report is made on twenty cases of urticaria, unresponsive to various types of antihistamines alone, but responsive to combined calcium antihistamine therapy.
2. Effects of such combined calcium antihistamine therapy on anaphylactoid reactions associated with urticaria are described.
3. A suggestion for further study of the pharmacodynamics between calcium and the histamine antihistamine phenomenon is made.

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1. Beeson, P. B., and Hoagland, C. L.: Proc. Soc. Exper. Biol. & Med., 38:160, (Feb.) 1938.
2. Blum, E.: Schweiz. Med. Wochenschr., 63:446, (May 13) 1933.
3. Cantarow, A.: Calcium Metabolism and Calcium Therapy. Ed. 2, p. 201. Philadelphia: Lea & Febiger, 1933.
4. Curphey, T. J., and Solomon, S.: New England J. Med., 214:150, (Jan 23) 1936.
5. Huff, Dick H.: Balyeat Clinic (Oklahoma) Proceedings, 19:6, (June) 1949.
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7. Strakosh, E. A.: Rocky Mountain M. J., 23:558, (July) 1946.

807 Carleton Building

Preliminary Program

GRADUATE INSTRUCTIONAL COURSE IN ALLERGY

February 9-11, 1951

and

SEVENTH ANNUAL CONGRESS

THE AMERICAN COLLEGE OF ALLERGISTS, INC.

February 11-14, 1951

Edgewater Beach Hotel

Chicago



NOTE: The papers will not necessarily be presented in the order indicated in this preliminary program. The titles of the papers and authors are also subject to change.



JOHN H. MITCHELL, M.D.
Columbus, Ohio
President, 1950-1951

Graduate Instructional Course in Allergy

FRIDAY, FEBRUARY 9, 1951

Morning Session—West Lounge

- 8:00-9:00 Registration
- 9:00-9:30 Orientation Lecture for All Registrants
JOHN D. GILLASPIE, M.D., Boulder, Colorado
- 9:30-10:00 Diagnostic Approach
History-taking
JOHN D. GILLASPIE, M.D., Boulder, Colorado
- 10:00-12:00 Skin Tests and Other Tests
MORRIS KAPLAN, M.D.; NORMAN J. EHRLICH, M.D., A. L. AARONSON, M.D., and Associates, Chicago, Illinois
Skin Tests
Direct
Scratch
Intracutaneous
Puncture
Indirect—Passive Transfer
Patch
Other Tests
Mucosal
Conjunctival
Ingestion
Inhalation
Injection
Instillation
Physical Allergy
Electrophoresis
Demonstration of Various Methods

12:00-2:00 LUNCH

Afternoon Session—West Lounge

DERMATOLOGIC ALLERGY

- 2:00-2:40 Pediatric Dermatology
JEROME GLASER, M.D., Assistant Professor of Pediatrics, University of Rochester School of Medicine and Dentistry, Rochester, New York
- 2:40-3:30 Atopic Eczema (Adults)
Neurodermatitis
MORRIS LEIDER, M.D., Assistant Clinical Professor of Dermatology and Syphilology, New York University Postgraduate Medical School, New York, New York
- 3:30-4:20 Urticaria, Angioneurotic Edema, and Purpura
NORMAN W. CLEIN, M.D., Children's Clinic; Clinical Assistant Professor of Pediatrics, University of Washington School of Medicine, Seattle, Washington
- 4:20-5:00 Eczema Dermatitis of the Contact Type
MORRIS LEIDER, M.D., Assistant Clinical Professor of Dermatology and Syphilology, New York University Postgraduate Medical School, New York, New York
- 5:00 Special Demonstration: Identification of Specific Allergen in Bacterial Allergy
HERMANN BLATT, M.D., Cincinnati, Ohio

SATURDAY, FEBRUARY 10, 1951

Morning Session—West Lounge

9:00-12:00 Nasal Allergy

ETHAN ALLAN BROWN, M.D., Lecturer in Allergy, Tufts College Medical School, Boston, Massachusetts
and Associates:

HAL M. DAVISON, M.D., Atlanta, Georgia
GILES A. KOELSCH, M.D., Rochester, Minnesota
HOMER E. PRINCE, M.D., Houston, Texas
OLIVER E. VAN ALYEA, M.D., Chicago, Illinois
ROGER P. WODEHOUSE, M.D., Pearl River, New York
Seasonal Hay Fever
 Pollinosis
 Molds
 Other Seasonal Dusts
Perennial Nasal Allergy
 (Diagnosis and treatment with the exception of methods of testing)

12:00-2:00 LUNCH

Afternoon Session—West Lounge

BRONCHIAL ASTHMA

2:00-2:30 Pathology

MILTON G. BOHRD, M.D.,* Director of Laboratories, Rochester General Hospital, Rochester, New York

2:30-4:30 Differential Diagnosis

LEON UNGER, M.D., Associate Professor of Medicine, Northwestern University Medical School, Chicago, Illinois, and Associates
Specific Therapy
Non-specific Therapy
Drug Therapy

4:30-5:00 Special Lecture on Status Asthmaticus

HENRY D. OGDEN, M.D., Clinical Assistant Professor of Medicine, Louisiana State University School of Medicine, New Orleans, Louisiana

SUNDAY, FEBRUARY 11, 1951

Morning Session—West Lounge

9:00-10:00 Gastrointestinal Allergy

ORVAL WITHERS, M.D., Associate Professor of Medicine, University of Kansas School of Medicine, Lawrence-Kansas City, Kansas

10:00-11:00 Food Allergy—Clinical Diagnosis and Management

ORVAL WITHERS, M.D., Associate Professor of Medicine, University of Kansas School of Medicine, Lawrence-Kansas City, Kansas

11:00-12:00 Vernal Conjunctivitis and Other Ocular Allergies

M. MURRAY PESHKIN, M.D., New York, New York

12:00-2:00 LUNCH

Afternoon Session—West Lounge

MISCELLANEOUS ALLERGIES

2:00-3:00 Ménière's Disease, Migraine and Other Allergic Headaches

JOHN H. MITCHELL, M.D., Assistant Clinical Professor of Medicine, Ohio State University College of Medicine, Columbus, Ohio

3:00-3:40 Cardiovascular System and Periarteritis Nodosa

FRED W. WITTICH, M.D., Minneapolis, Minnesota

3:40-4:00 Urinary Tract

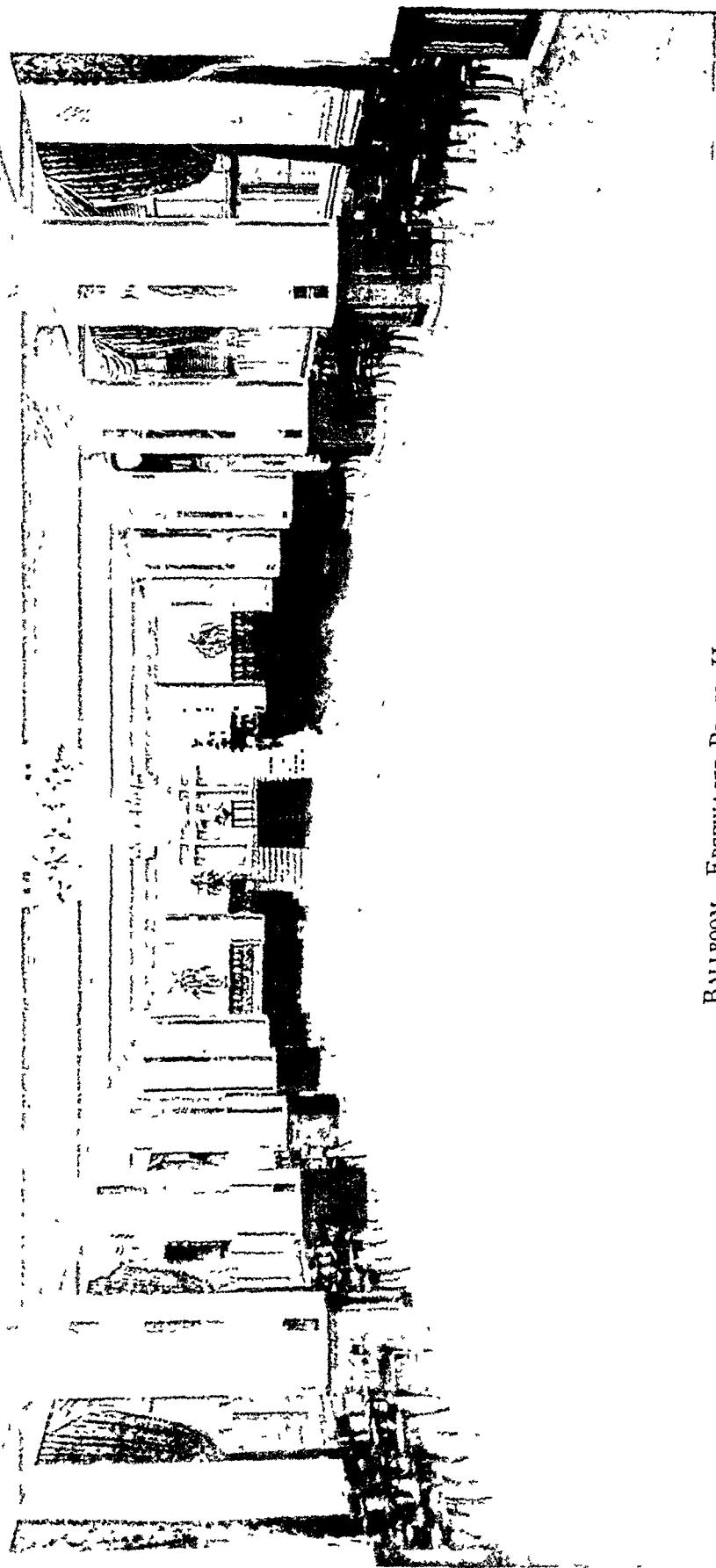
SUSAN C. DEES, M.D., Associate Professor of Pediatrics and Allergy, Duke University School of Medicine, Durham, North Carolina

4:00-5:00 Newer Knowledge in the Therapy of Allergic Diseases (ACTH)

HERON G. RANDOLPH, M.D., Instructor in Medicine, Northwestern University Medical School, Chicago, Illinois

*By invitation

SEVENTH ANNUAL CONGRESS
THE AMERICAN COLLEGE OF ALLERGISTS, INC.
February 11-14, 1951
Edgewater Beach Hotel
Chicago



BALLROOM—ENGEWAYER BEACH HOTEL

Seventh Annual Congress

SUNDAY, FEBRUARY 11, 1951

2:00 p.m. Registration—The Foyer

MONDAY, FEBRUARY 12, 1951

Morning Session—The Ballroom

GENERAL SESSION

Chairman: JOHN D. GILLASPIE, M.D., Boulder, Colorado

- 9:00-9:10 The Diagnosis and Treatment of Bacterial Allergy
HERMANN BLATT, M.D., Cincinnati, Ohio
- 9:20-9:30 House Dust as a Cause and Carrier of Disease
ALBERT H. UNGER, M.D., Clinical Assistant, Northwestern University Medical School; Attending Staff, Columbus Hospital, Chicago, Illinois
- 9:40-9:50 Comparison of Anamnestic Therapy with Perennial and Preseasonal Therapy in the Treatment of Pollinosis
LEWIS E. ABRAM, M.D., and JEROME S. FRANKEL, M.D., Cleveland, Ohio
- 10:00-10:10 Present Status of the Use of Ergot in Migraine
LESTER S. BLUMENTHAL, M.D.* Clinical Instructor in Medicine, George Washington University Hospital; Attending Physician, George Washington and Gallinger Municipal Hospitals; Chief of the Headache Clinic, George Washington University Hospital, Washington, D. C.
- MARVIN FUCHS, M.D.,* Clinical Instructor in Medicine, George Washington University School of Medicine; Attending Physician, George Washington and Gallinger Municipal Hospitals; Associate in the Allergy and Headache Clinics, George Washington University Hospital, Washington, D. C.
- 10:20-10:30 Allergic Aspects of Psychiatry
THERON G. RANDOLPH, M.D., Instructor in Medicine, Northwestern University Medical School, Chicago, Illinois

* * *

There will be a 10-minute discussion following each paper.

10:30-11:00 RECESS TO VISIT EXHIBITS

- 11:00-11:10 Studies of the 11-Oxycorticosteroids of Allergic Patients Treated with ACTH (Armour)
ALLAN J. STANLEY, Ph.D.,* Department of Physiology, University of Oklahoma School of Medicine and University Hospitals
GEORGE S. BOZALIS, M.D., Department of Internal Medicine, University of Oklahoma School of Medicine and University Hospitals, Oklahoma City, Oklahoma
in collaboration with
DICK H. HUFF, M.D., VERNON D. CUSHING, M.D., and LEO CAWLEY, M.D.
- 11:10-11:20 ACTH in the Treatment of Hay Fever
MICHAEL ZELLER, M.D., Clinical Instructor in Medicine, University of Illinois College of Medicine, Chicago, Illinois
- 11:20-11:30 Observations on the Use of ACTH and Cortisone in the Treatment of Hay Fever and Asthma
SIDNEY FRIEDLAENDER, M.D., Instructor in Clinical Medicine, Wayne University College of Medicine, Detroit, Michigan
ALEX S. FRIEDLAENDER, M.D., Instructor in Clinical Medicine, Wayne University College of Medicine, Detroit, Michigan

*By invitation

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2:00	8:35
3:25	9:05
3:55	9:35
4:40	10:25
5:15	10:55
5:45	11:45

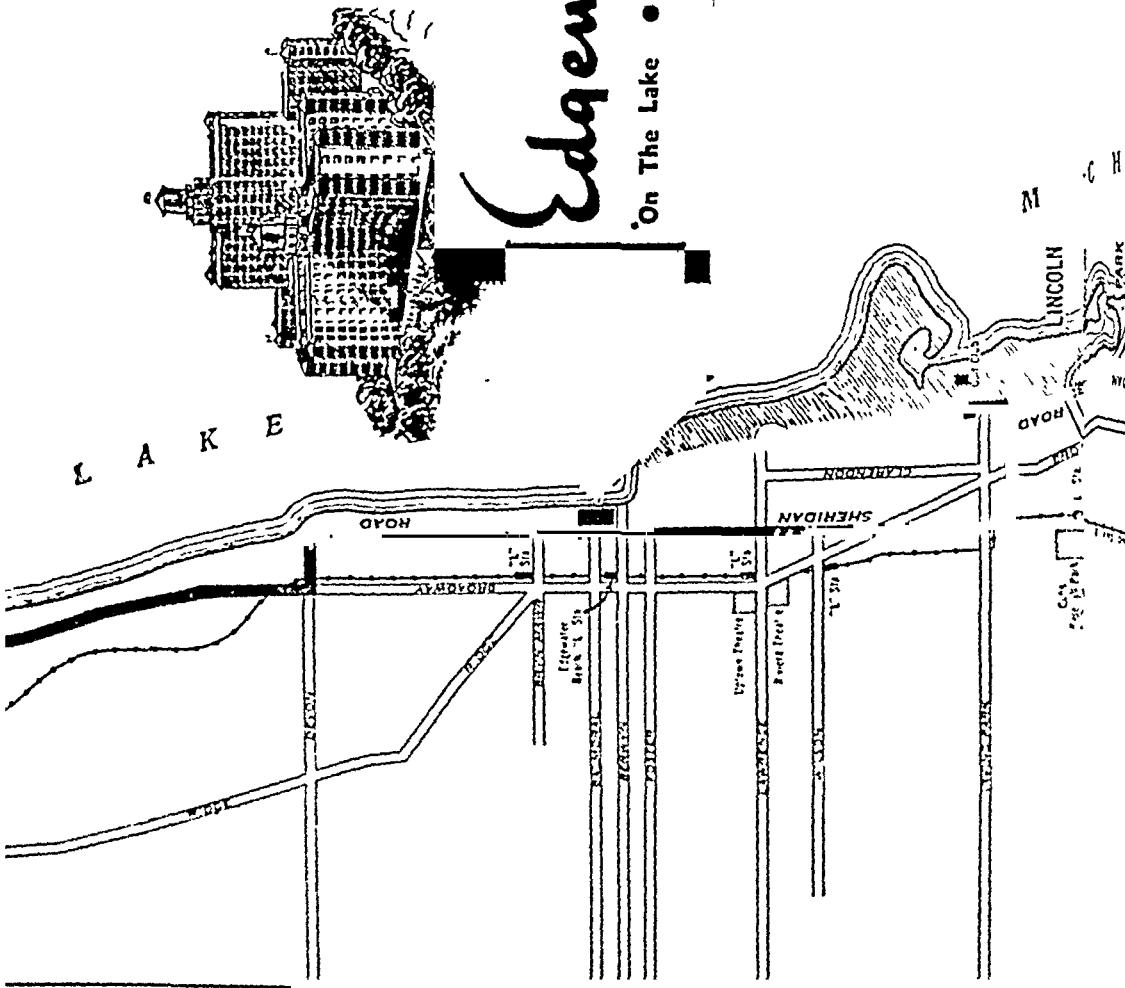
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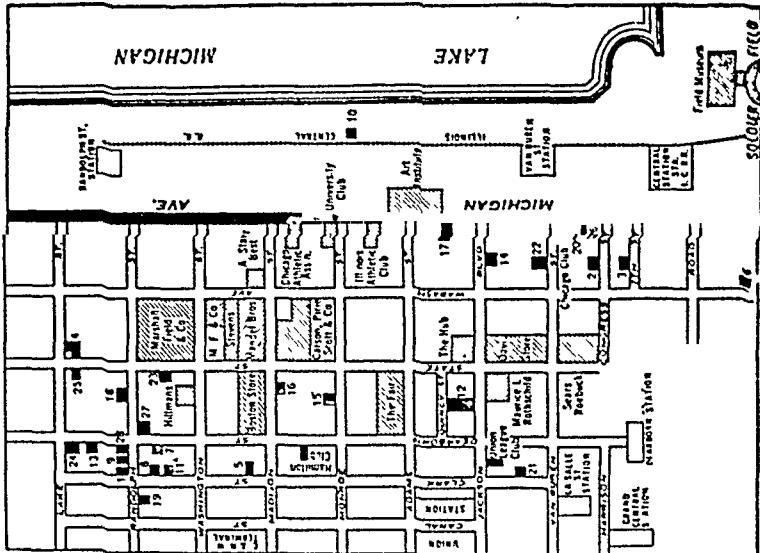
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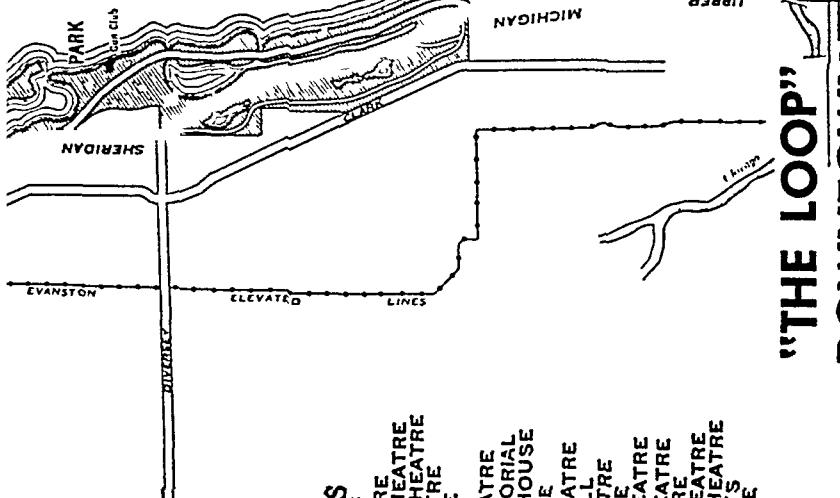


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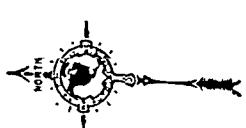
C H I C A G O



"THE LOOP" DOWNTOWN CHICAGO

THEATRES

- 1 APOLLO THEATRE
- 2 AUDITORIUM THEATRE
- 3 BLACKSTONE THEATRE
- 4 CHICAGO THEATRE
- 5 CLARK THEATRE
- 6 COLISEUM
- 8 ERLANGER THEATRE
- 10 GOODMAN MEMORIAL
- 11 GRAND OPERA HOUSE
- 13 HARRIS THEATRE
- 16 MCKICKERS THEATRE
- 17 ORCHESTRA HALL
- 18 ORIENTAL THEATRE
- 19 PALACE THEATRE
- 20 PLAYHOUSE THEATRE
- 23 ROOSEVELT THEATRE
- 24 SELWYN THEATRE
- 25 STATE LAKE THEATRE
- 26 STUDESAKER THEATRE
- 27 UNITED ARTISTS
- 28 WOODS THEATRE



- 11:30-11:40 Studies on the Therapeutic Effects of ACTH and Cortisone in Asthma and Other Allergic Conditions

BRAM ROSE, M.D.,* Associate Professor of Medicine, McGill University, Montreal, Canada
in collaboration with
J. A. P. PARE, M.D., K. K. PUMP, M.D., and R. L. STANFORD, M.D., Montreal, Canada

- 11:40-11:50 The Use of ACTH in Ambulatory Patients with Severe Bronchial Asthma

ETHAN ALLAN BROWN, M.D., Lecturer in Allergy, Tufts College Medical School, Boston, Massachusetts

* * *

Open discussion will be held following the ACTH symposium.

LUNCH

Afternoon Session—The Ballroom

SECTION ON PSYCHOSOMATIC ALLERGY

Chairman: HAROLD A. ABRAMSON, M.D., New York City

- 2:00-2:15 Some Psychological Aspects of the Treatment of Patients Who Have Food Allergies

WILLIAM KAUFMAN, Ph.D., M.D., Bridgeport, Connecticut

- 2:25-2:40 An Asthmatic Death in Which Psychic Influences Were an Aggravating Factor. Case Report.

REDFORD A. WILSON, M.D., Tucson, Arizona
and
JAMES A. SUTTON, M.D., Tucson, Arizona

- 2:30-3:05 The Role of the Specialist in Psychotherapy

FRANK FREMONT-SMITH, M.D.,* Medical Director, The Josiah Macy, Jr., Foundation, New York, New York

- 3:15-3:45 RECESS TO VISIT EXHIBITS

- 3:45-4:00 The Genesis and Treatment of a Recurrent Attack of Asthma

HYMAN MILLER, M.D., Beverly Hills, California
and
DOROTHY BARUCH, Ph.D.,* Beverly Hills, California

- 4:10-4:25 Psychotherapy in Multiple Sclerosis

HINTON D. JONEZ, M.D., Medical Director, Multiple Sclerosis Clinic, St. Joseph's Hospital, Tacoma, Washington

- 4:35-4:50 Technic for Screening Verbatim Psychotherapeutic Recordings and Its Application to Allergic Patients

HAROLD A. ABRAMSON, M.D., Chief, Allergy Clinic, Mt. Sinai Hospital, New York, New York

- 5:00-5:15 Combined Allergic and Psychosomatic Treatment in Bronchial Asthma

ETHAN ALLAN BROWN, M.D., Lecturer in Allergy, Tufts College Medical School, Boston, Massachusetts

* * *

There will be a 10-minute discussion following each paper.

Evening—West Lounge

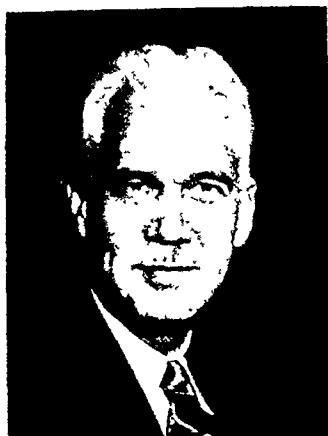
- 6:00 **Cocktail Party**
Courtesy of the SCHERING CORPORATION, Bloomfield, New Jersey
- 7:00 **Color Movies: Light Plane Caravan to Guatemala**
HERMAN HEISE, M.D., Milwaukee, Wisconsin

TUESDAY, FEBRUARY 13, 1951

Morning Session—The Ballroom

- 9:00 **Presidential Address**

JOHN H. MITCHELL, M.D., Assistant Clinical Professor of Medicine, Ohio State University College of Medicine, Columbus, Ohio



ARILD E. HANSEN

- 10:00 **Recess**
- 10:15 **Business Meeting**
- 12:30 **Dinner-Luncheon in the Marine Dining Room**

Afternoon Session—The Ballroom

SECTION ON PEDIATRICS

Chairman: BERT RATNER, M.D., New York City

- 2:00-2:15 **Milk Allergy in Infants**
NORMAN W. CLEIN, M.D., Children's Clinic; Clinical Assistant Professor of Pediatrics, University of Washington School of Medicine, Seattle, Washington
- 2:25-2:40 **Experiences with ACTH in the Treatment of Asthma and Eczema in Infancy and Childhood***
JEROME GLASER, M.D., Assistant Professor of Pediatrics, University of Rochester School of Medicine and Dentistry; Pediatrician-in-Chief, Genesee Hospital, Rochester, New York
- 2:50-3:05 **Management of Asthma in Infancy**
STANLEY S. FREEDMAN, M.D., Providence, Rhode Island

*Authors of paper: JEROME GLASER, M.D.; SHELDON C. SIEGEL, M.D.; JACOB D. GOLDSTEIN, M.D.; and RICHARD S. MELTZER, M.D., Rochester, New York.

3:15-3:45 RECESS TO VISIT EXHIBITS

3:45-4:00 Allergic Epilepsy

SUSAN C. DEES, M.D., Associate Professor of Pediatrics and Allergy,
Duke University School of Medicine, Durham, North Carolina
and

HANS LOWENBACH, M.D.,* Associate Professor of Neuropsychiatry,
Duke University School of Medicine, Durham, North Carolina

4:10-4:25 The Present Status of Pediatric Allergy

BRET RATNER, M.D., Professor of Clinical Pediatrics, New York
Medical College, New York, New York

4:35-4:50 Antihistaminic Poisoning in Children

HAROLD I. LECKS, M.D.,* Assistant Allergist, Children's Hospital,
Philadelphia, Pennsylvania; Instructor in Pediatrics, University of
Pennsylvania Medical School, Philadelphia, Pennsylvania

5:00-5:10 Repository Penicillin Injections in Allergic Children

SAMUEL J. LEVIN, M.D., Detroit, Michigan

5:20-5:35 Ragweed Pollinosis—a Public Health Problem in School Children

SHELDON C. SIEGEL, M.D.,* Instructor in Pediatrics, University of
Rochester School of Medicine and Dentistry, Rochester, New York

5:35-5:45 Skeletal Abnormalities Commonly Associated with Allergic Disorders

NORMAN A. POKORNY, M.D., Springfield, Massachusetts

* * *

There will be a 10-minute discussion following each paper.

Evening Session—Michigan Room

COMMITTEE ON DERMATOLOGIC ALLERGY

Chairman: STEPHAN EPSTEIN, M.D., Marshfield, Wisconsin

DERMATOLOGY ROUND TABLE

Moderator: RUDOLF L. BAER, M.D.,† New York City

7:30 P.M.

Participants:

HERBERT RATTNER, M.D.,* Associate Professor of Dermatology, Northwestern University Medical School, Chicago, Illinois

STEPHEN ROTHMAN, M.D.,* Professor of Dermatology, University of Chicago, Chicago, Illinois

JAMES R. WEBSTER, M.D.,* Professor of Dermatology, Northwestern University Medical School, Chicago, Illinois

MORRIS LEIDER, M.D., Assistant Clinical Professor of Dermatology and Syphilology, New York University Postgraduate Medical School, New York, New York

ADOLPH B. LOVEMAN, M.D., Assistant Clinical Professor of Dermatology and Syphilology, University of Louisville School of Medicine, Louisville, Kentucky

STEPHAN EPSTEIN, M.D., Marshfield Clinic, Marshfield, Wisconsin; Clinical Associate Professor of Dermatology, University of Minnesota Medical School, Minneapolis, Minnesota

ADOLPH ROSTENBERG, JR., M.D., Assistant Professor of Dermatology and Associate Director of the Allegy Unit, Illinois College of Medicine, Chicago, Illinois

NOTE: This is a question and answer round table. Please submit questions at least one day in advance at the Registration Desk, marking questions for the attention of Moderator Rudolf L. Baer, M.D.

Following the round table, there will be an informal gathering of those members of the College who are interested in dermatology, for the purpose of starting a permanent Dermatologic Group within the College.

*By invitation
†RUDOLF L. BAER, M.D., Associate Professor of Clinical Dermatology and Syphilology, New York University Postgraduate Medical School, New York, New York.

WEDNESDAY, FEBRUARY 14, 1951

Morning Session—The Ballroom

SECTION ON OTOLARYNGOLOGY

Chairman: GEORGE E. SHAMBAUGH, JR., M.D., Chicago, Illinois

9:00-10:15 SYMPOSIUM

Sinus Versus Allergic Headache

GEORGE E. SHAMBAUGH, JR., M.D., Associate Professor of Otolaryngology, Northwestern University Medical School, Chicago, Illinois

Histamine and Headache

FRENCH K. HANSEL, M.D., Director, Hansel Foundation; Associate Professor Clinical Otolaryngology-Laryngology, Washington University School of Medicine, St. Louis, Missouri

Ocular Headache

ALBERT D. RUEDEMANN, M.D.,* Professor of Ophthalmology, Wayne University College of Medicine, Detroit, Michigan

10:15-10:45 RECESS TO VISIT EXHIBITS

SECTION ON DERMATOLOGY

Chairmen: MORRIS LEIDER, M.D.,† and RUDOLF L. BAER, M.D.,‡ New York City

10:45-11:00 Periorbital Dermatitis

BOEN SWINNY, M.D., San Antonio, Texas

11:10-11:20 Urticaria Due to Pollen

GEORGE L. WALDBOTT, M.D., Detroit, Michigan
in collaboration with
KARL MERKLE, M.D.,* Detroit, Michigan

11:30-11:40 Sensitivity Patterns in Ragweed Dermatitis

S. M. MACKOFF, M.D.,* Department of Dermatology, University of Minnesota, Minneapolis, Minnesota
in collaboration with
A. ORVILLE DAHL, M.D.,* Professor of Botany, University of Minnesota, Minneapolis, Minnesota

11:50-12:00 Infantile Eczema in a Rural District—A Ten-year Study

STEPHAN EPSTEIN, M.D., Marshfield Clinic, Marshfield, Wisconsin;
Clinical Associate Professor of Dermatology, University of Minnesota Medical School, Minneapolis, Minnesota
with the assistance of
MARIE PALECEK, R.N.

* * *

There will be a 10-minute discussion following each paper.

*By invitation

†MORRIS LEIDER, M.D., Assistant Clinical Professor of Dermatology and Syphilology, New York University Postgraduate Medical School, New York, New York.

‡RUDOLF L. BAER, M.D., Associate Professor of Clinical Dermatology and Syphilology, New York University Postgraduate Medical School, New York, New York.

LUNCH

Afternoon Session—The Ballroom

PANEL: RHEUMATISM AND ARTHRITIS

Chairman: GEORGE E. ROCKWELL, M.D., Milford, Ohio

2:00-2:10 The Over-all Picture of Rheumatism and Arthritis

WILLIAM KAUFMAN, Ph.D., M.D., Bridgeport, Connecticut

2:10-2:30 Pathology of Rheumatism and Arthritis

M. G. BOHROD, M.D.,* Director of Laboratories, Rochester General Hospital, Rochester, New York

2:30-2:40 Food Allergy as a Factor in Rheumatoid Arthritis

MICHAEL ZELLER, M.D., Clinical Instructor in Medicine, University of Illinois College of Medicine, Chicago, Illinois

2:40-3:10 Physiologic, Metabolic, and Toxic Effects of ACTH and Cortisone

THOMAS F. DOUGHERTY, Ph.D.,* Professor and Chairman, Department of Anatomy, University of Utah School of Medicine, Salt Lake City, Utah

3:10-3:40 RECESS TO VISIT EXHIBITS

3:40-3:55 Clinical Use of ACTH and Cortisone

HERON G. RANDOLPH, M.D., Instructor in Medicine, Northwestern University Medical School, Chicago, Illinois

3:55-4:05 Chemical Agents Which May Be Used in Therapy as Substitutes for ACTH and/or Cortisone

C. R. K. JOHNSTON, M.D., Head of Department of Allergy, Cleveland Clinic, Cleveland, Ohio

* * *

The Panel will be followed by a round table discussion.

*By invitation

IF TIME PERMITS

The Acid-Anoxia-Endocrine Theory of Allergy

HARRY G. CLARK, M.D.,* and THERON G. RANDOLPH, M.D., Chicago, Illinois

The Clinical Evaluation of Ambodryl Hydrochloride

J. WARRICK THOMAS, M.D., and FRANK R. KELLY, JR., M.D.,* Richmond, Virginia

Standardization of Pollen Extracts by Precipitin

ROGER P. WODEHOUSE, M.D., Pearl River, New York

TO BE READ BY TITLE

Treatment of Certain Dermatoses as Bacterial Allergies

K. A. BAIRD, M.D., West Saint John, New Brunswick, Canada

Natural Steroid Complex in the Treatment of Bronchial Asthma

S. H. JAROS, M.D., and AARON D. SPIELMAN, M.D., New York, New York

Survey of Air-borne Fungus Spores of the Boston Area in Relation to Inhalant Allergies

LEO KAPLAN, Ph.D.,* Carbondale, Illinois

The Treatment of Certain Allergic Syndromes with Parenteral Diphenhydramine Hydrochloride

WILLIAM H. LIPMAN, M.D., Kenosha, Wisconsin

The Single Injection Treatment of Hay Fever. Study IV

A. L. MAIETTA, M.D., Boston, Massachusetts

Mold Fungi in the Etiology of Respiratory Allergic Diseases. XV. Further Survey Studies

MARIE BETZNER MORROW, Ph.D., Austin, Texas

A New Method and Medium for Administering and Controlling the Action of Therapeutic Agents with Particular Reference to Epinephrin

ROY A. OVER, M.D., San Diego, California

Newer Drugs and Their Use in Allergy

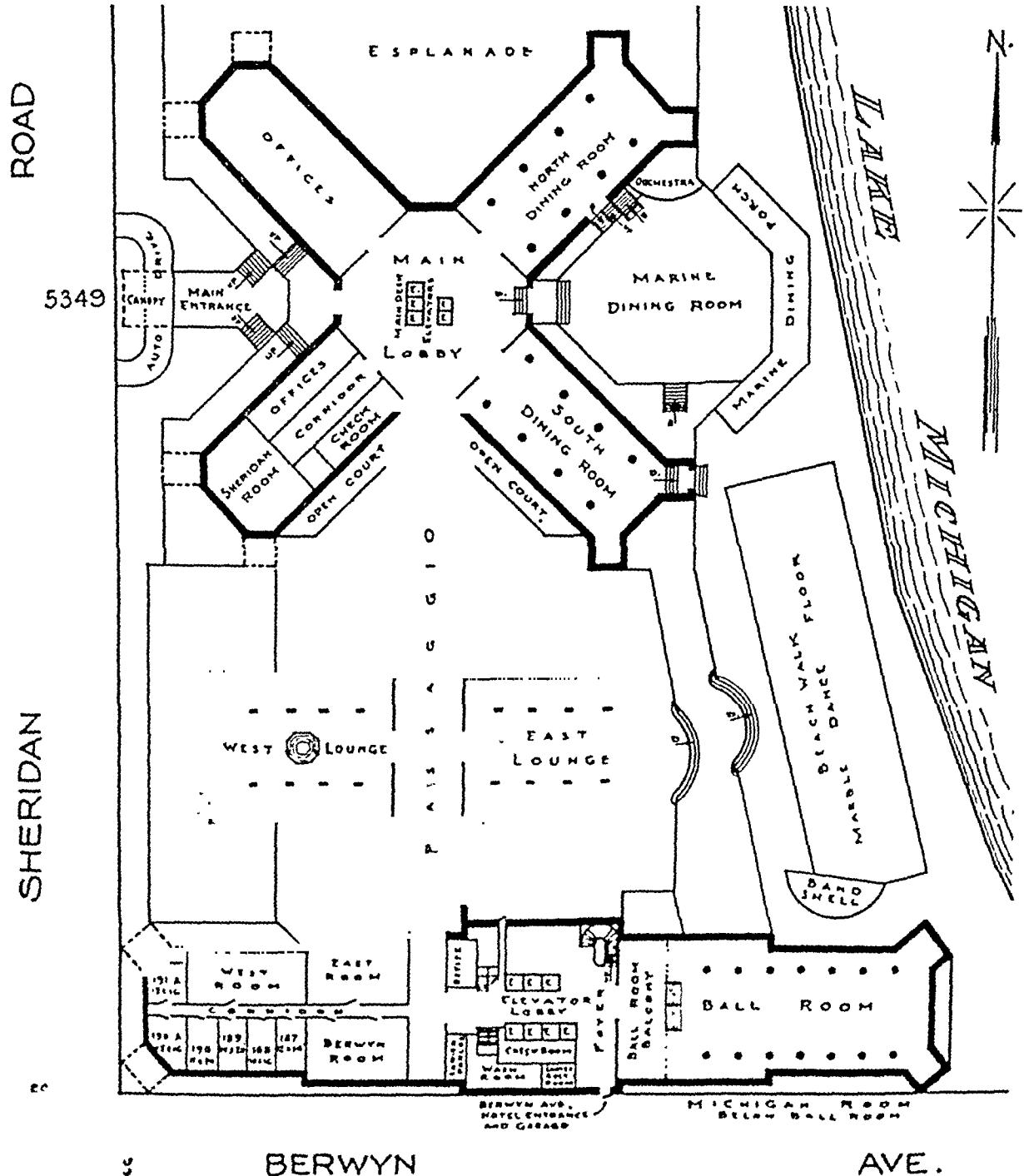
JOSEPH H. SHAFFER, M.D.,* Detroit, Michigan

The Gothlin Index in Allergic Disease

HYMAN SHERMAN, M.D., Brooklyn, New York; JEROME SHERMAN, M.D.,* Baltimore, Maryland; THEODORE D. COHN, M.D.,* Brooklyn, New York

*By invitation

MAIN FLOOR PLAN • EDGEWATER BEACH HOTEL
Showing Location of Public Rooms, Dining Rooms, Lobby, Etc.



S

BERWYN

AVE.

THE USE OF DIBENAMINE IN THE SEVERE ASTHMATIC STATE AND RELATED CHRONIC PULMONARY CONDITIONS

S. D. KLOTZ, M.D., and CLARENCE BERNSTEIN, M.D., F.A.C.A., F.A.A.A.
Orlando, Florida

ALTHOUGH the therapy for severe asthmatic states has improved markedly in recent years with the advent of epinephrine and related sympathomimetic drugs, aminophylline and similar derivatives, antibiotics, aerosol mechanisms, et cetera, there are frequent instances when additional therapeutic help is most urgently needed.

Recently several groups of "adrenergic blocking agents" have been synthesized which specifically inhibit certain responses of effector cells to epinephrine, to related amines, and to sympathetic nerve impulses. One such group belongs to the B-haloalkylamine series, of which Dibenamine (*N,N*-Dibenzyl-B-chlorethylamine) Chloride may be considered as the prototype. At the present time, the blockade produced by members of this group of compounds appears to be more complete and specific than that produced by members of other series.

The most prominent action of Dibenamine is a specific blockade of certain excitatory responses to epinephrine and sympathetic nerve activity. Pressor responses to exogenous and endogenous epinephrine are blocked and reversed in most animals. Dibenamine provides marked protection against lethal effects of epinephrine. Depression of the central nervous system does not appear to be a significant factor in the inhibition of vaso-motor reflexes, for it appears to be adequately established that the drug is devoid of actions on the autonomic ganglia and on reflex pathways in the central nervous system. Dibenamine does not block or reverse the inhibitory sympathetic functions. Smooth muscles which are relaxed by epinephrine or sympathetic stimulation are uninfluenced.

It is of both theoretical and practical interest that certain Dibenamine derivatives produce not only adrenergic blockade but are also antagonistic to histamine, as shown by Loew and Nickerson and their respective co-workers.^{5,7} Some of the compounds examined are many times more potent in animals than are the antihistaminic drugs currently employed in therapeutics. They are also characterized by remarkably long duration of antihistaminic action. Speculation as to the chemical basis and pharmacological import of the concomitance of anti-adrenergic and antihistaminic actions must be clarified by further investigations.

In the over-all picture of the severe asthmatic state, with its anoxia and accompanying pulmonary arterial hypertension, pallor, sweating, rapid thready pulse, marked anxiety, and finally terminal exhaustion with shock-like syndrome, it appeared to us that certain of these features were

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not only not useful but were even harmful. If a drug with the properties of Dibenamine could block the noxious "pressor" effects of endogenous epinephrine and exogenous epinephrine derivatives without at the same time losing the desired inhibitory action on the smooth muscle of the bronchial tree, such a drug would be a valuable adjunct in potentiating the action of adrenaline in severe asthma, particularly in so-called "adrenaline-fast" states.

METHOD AND RESULTS

Dibenamine was administered to twenty patients with severe bronchial asthma. Six of these were in status asthmaticus and had become resistant to epinephrine, to related sympathomimetic drugs, and to the other usual therapeutic agents. Four patients had a chronic pulmonary pathologic condition with an associated cor pulmonale, anoxia, and bronchospastic features. All had been under treatment for two or more days with the customary therapy with little relief or with actual deterioration in their condition. After the second day of controlled observation, Dibenamine was additionally administered.

Dibenamine* can be given either orally or intravenously. For the oral route, it was supplied in the form of coated tablets, each containing 130 mg (2 grains). Dosage varied from one or two tablets every three to four hours. For intravenous medication a sterile 5 per cent solution in alcohol—propylene glycol, each cubic centimeter containing 50 mg of Dibenamine—was diluted into a 300 to 500 cc unit of normal saline, or 5 per cent glucose, infusion. Dosage was calculated at 5 to 7 mg per kg of body weight, with rate of flow adjusted so that the intravenous infusion required not less than sixty minutes. Since Dibenamine and other B-haloalkyl groupings are related to the nitrogen mustard series, there is local tissue damage if given via subcutaneous, intramuscular or intraperitoneal routes. There is some local irritation with oral administration, and in some instances this interferes greatly in its therapeutic effect.

In all cases except two, the oral route was employed. Practically *every* patient (in whom therapeutic levels of the drug could be attained) experienced subjective relief within eight to fourteen hours. There was a marked decrease in anxiety, dyspnea, and tightness of the chest. The pale and anxious patient with cold perspiration and thready peripheral pulse was gradually and occasionally rapidly returned to a normal status. Pulsus paradoxicus, frequently seen in many of the severe asthmatics, quickly improved or disappeared altogether. There was marked amelioration in the patients' vital capacity along with clearing of the typical auscultatory findings in the chest. Usually within forty-eight hours the patients were comfortable, whereas previously some had been in almost continuous severe distress for two or three weeks. Most of the patients' systemic blood pressure readings were low to normal with little change following

* Manufactured for experimental uses by Smith, Kline & French Company.

Dibenamine. No major complications caused by the drug were noted. Some of the patients had vague mental excitation which resembled in some respects that seen in procaine excitement. The most frequent adverse side reaction was nausea with or without vomiting, which, unless too severe, did not detract from the clinical effectiveness of the drug but thereby possibly added an adjuvant expectorant action. In several patients, because of vomiting, adequate dosage levels could not be attained or the drug had to be discontinued. At present we are trying to solve this problem by the use of gastric anesthetic-sedative agents and demulcents, or by combination with procaine. In many of our chronic but less severe cases, we have overcome the nausea by starting with a small oral dose and gradually increasing to tolerance. One of the most acutely ill patients came under our care with severe vomiting caused by an injection of morphine to which she had an idiosyncrasy. Following Dibenamine intravenously, her nausea and vomiting persisted for another thirty-six hours. That Dibenamine contributed to its persistence is a strong probability.

DISCUSSION

Many clinicians agree in the belief that there is an altered reaction to epinephrine in many of the patients with bronchial asthma. H. Abramson in his discussion of the psychosomatic aspects of asthma states that an undcurrent of anxiety exists in all of these cases and feels that many of such patients tolerate sympathomimetic drugs poorly. Cameron¹ feels that through long stress the individual's tendency to develop tension has become so augmented—both with regard to the ease with which the reaction is elicited and with regard to its intensity—as to make the small hour-to-hour stress of daily living, formerly barely noticed, sufficient in the now over-reactive individual to perpetuate his symptoms. His anxiety states have now become self-sustaining. Subsequent dealing with primary causes can no longer remove completely the autonomous sequences. Cameron tried to interrupt such sequences by decreasing the general reactivity of the individual by means of desensitizing doses of epinephrine.

Curry et al² study the effect of another adrenergic blocking agent, Dihydroergocornine, on pulmonary responses to histamine and methacholine in subjects with bronchial asthma. Previous reports had shown that interruption of the sympathetic nervous system in the lung brings about cessation of asthmatic attacks in certain individuals, as with procaine block of the sympathetic pathways. Their results indicated that in some cases the sympatholytic agent furnished remarkable protection against the pulmonary reaction to histamine and methacholine.

Motley³ has shown that anoxia causes pulmonary vasoconstriction. There is a rise of pulmonary artery pressure due to stasis of the smaller pulmonary vessels and pulmonary arterioconstriction. Zimmerman¹⁰ has measured the pulmonary artery pressure in human beings in severe asthma and found the pressure elevated in all cases.

Koenig and Koenig⁴ in a recent study of pulmonary edema produced in animals by toxic doses of ammonium salts found that this pulmonary edema could be prevented by low cervical and high thoracic spinal cord transections, by the "alarm reaction," and by Dibenamine. This was felt to be strong evidence for the importance of sympathetic impulses in this phenomenon. Blocking parasympathetic nerve impulses was ineffectual in preventing this edema. Recent experiments⁸ in dogs have now demonstrated that adrenergic blockade with Dibenamine provides marked protection against both hemorrhagic and traumatic shock. This protection is largely due to the elimination of reflex vasoconstriction which ordinarily sustains blood pressure at the expense of blood flow. Recent work suggests that there are adrenergic and cholinergic agents secreted by the hypothalamus, neurohypophysis and proximal portions of the adenohypophysis, whence they are carried via the hypophyseal portal circulation to the pars distalis of the adenohypophysis.³ While it has not been shown that adrenergic blocking agents inhibit responses of the central nervous system to adrenergic stimuli, yet the probable value of the elimination of excessive adrenergic stimuli to the brain centers has not to our knowledge been thoroughly investigated. Rockwell,⁹ however, has reported benefit from Dibenamine in certain psychopathologic syndromes associated with markedly increased anxiety and abnormal blood levels of adrenaline.

No ideal blocking adrenergic agent is as yet available, but compounds with improved specificity and potency are rapidly being developed. At present, Dibenamine appears to be the most effective drug available. Its value in severe bronchial asthma and chronic pulmonary diseases with anoxia first suggested itself on the theoretical possibility that it might correct certain of the pathologic-physiologic alterations produced within the body by these states. In a majority of instances, the clinical result confirmed our most enthusiastic expectations; in some, less striking alterations were noted. We present our findings at this time with the hope that other allergy researchers may become interested in this new therapeutic adjunct which may prove very useful in a most difficult clinical entity.

SUMMARY

1. Dibenamine, a new adrenergic blocking agent, was used as a therapeutic adjunct in cases of severe bronchial asthma and chronic pulmonary diseases with anoxia with some excellent results.
2. Dibenamine is felt to be of value in these states by virtue of its sympathoadrenolytic effect which reverses the vasoconstrictor responses to epinephrine but does not alter its inhibitory effect on the bronchial musculature. In this manner the increased pulmonary arterial tension and congestion that develop are decreased, and consequently both the pulmonic and systemic circulations are improved.

3. Dibenamine appears also to increase markedly the body tolerance for sympathomimetic substances as well as the sensitivity to their inhibitory effects, a property that may be of particular help in so-called "adrenalin-fast" states.

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740 Magnolia Avenue

SEVERE SERUM-SICKNESS TYPE OF PENICILLIN REACTION

(Continued from Page 753)

5. Because of its ability to sensitize penicillin should not be used indiscriminately. Its use should be reserved for those cases when the physician feels that not to do so would be jeopardizing the health of his patient.

6. A severe case of delayed serum sickness following penicillin, which did not yield to any of the known antihistaminic drugs, has been reported together with a brief review of the literature of similar cases.

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741 Madison Avenue

PREGNANCY AND THE TREATMENT OF HAY FEVER, ALLERGIC RHINITIS, AND POLLEN ASTHMA

SAUL W. CHESTER, M.D., F.A.C.A.

Paterson, New Jersey

THE LITERATURE on the treatment of allergies that existed or appear during pregnancy is indeed meager. Ratner¹ states that it is the general consensus that females do not lose their sensitivities during gestation. Urbach² states that the assumed presence of antibodies in the pregnant woman serves to explain the good results achieved with systemic injections of the serum of pregnant women in the treatment of the dermatoses of pregnancy. Waldbott and Bailey³ demonstrated improvement in some menstrual asthmas with estrogenic therapy. No mention is made of the treatment of pollerosis, vasomotor rhinitis, or pollen asthma complicated by pregnancy. Since 1935 I have been treating pregnant women suffering from pollerosis, vasomotor rhinitis, and pollen asthma with consistently good average results. At no time were constitutional reactions obtained, and all were delivered in the usual manner with no fatalities. In all, twenty cases are presented: nine primipara and eleven multipara.

TABLE I

Name Age	Prima- para	Multi- para	History	Diagnosis	Date treatment started	Peren- nial	Date of delivery	Compli- cations
Mrs. R.M. 26 years	X		Pollen asthma 1 year	Ragweed hay fever and chronic urticaria	1/5/35	X	12/5/36	None
Mrs. S.Y. 21 years		2 3 4 5	Pollerosis and pollen asthma 4 years	Pollerosis and pollen asthma	1/2/34	X	10/31/36 8/18/39 2/3/43 7/19/45	None None None None
Mrs. T.D. 32 years		2	Hay fever and asthma 10 years	Pollerosis (ragweed) and pollen asthma	1/2/36	X	2/1/37	None
Mrs. S.R. 22 years	X		Hay fever 5 years	Pollerosis (grass and ragweed)	2/3/36	X	3/18/37	None
Mrs. A.O.S. 23 years	X		Hay fever 4 years	Pollerosis (ragweed)	2/10/40	X	3/5/41	None
Mrs. O.Y. 29 years		2	Hay fever 3 years	Pollerosis (ragweed) and dust sensitivity	5/3/43	X	11/22/43	None
Mrs. A.I. 22 years	X		Hay fever and asthma 5 years	Pollerosis (grass and ragweed), pollen asthma	1/3/40	X	2/1/43	None
Mrs. G.C. 26 years	X		Hay fever 2 years	Pollerosis (grass and ragweed)	10/20/47	X	11/28/47	None
Mrs. E.M. 31 3/37	b	6	Hay fever and asthma 7 years	Ragweed pollen asthma, vaso- motor rhinitis	10/30/45	X	8/31/46	None

PREGNANCY—CHESTER

TABLE I (continued)

Name Age	Prima- para	Multi- para	History	Diagnosis	Date treatment started	Peren- nial	Date of delivery	Compli- cations
Mrs. C.R. 25 years		1	Hay fever 9 years	Pollenosis (grass and dust)	1/25/47	X	7/17/47	Lost first child received treatment at that time
							at birth; no trea	
Mrs. L.B. 28 years		2	Hay fever 10 years	Pollenosis (grass and ragweed), dust sensi- tivity	4/26/44	X	7/12/48	None
Mrs. D.C. 40 years		2	Asthma and vasomotor rhinitis 4 years	Asthma and vasomotor rhinitis	7/12/48	X	1/6/49	None
Mrs. C.D. 26 years		3	Hay fever and asthma 10 years	Pollenosis and pollen asthma	10/7/48	X	7/15/49	None
Mrs. M.O. 26 years	X		Grass hay fever and vaso- motor rhinitis	Pollenosis and vasomotor rhinitis	8/5/48	X	2/6/49	None
Mrs. I.G. 24 years		1	Hay fever 4 years	Pollenosis (grass and ragweed)	1/2/46	X	2/15/49	None
Mrs. F.J.M. 25 years	X		Hay fever 1 year Hives 3 years	Pollenosis (grass and ragweed), chronic urticaria	2/16/44	X	6/2/49	None
Mrs. O.D. 25 years		2	Erythema, pruritis, vasomotor rhinitis 3 years	Pruritus, vasomotor rhinitis	2/3/47	X	6/2/48	Lost first child at term; no treat- ment
Mrs. J.L.D. 29 years		2	Spring and fall hay fever 3 years Eczema at age 14; left her at 16	Pollenosis (grass and ragweed)	2/7/44	X	11/12/46	None
Mrs. M.L.	X		Hay fever 4 years	Pollenosis (grass and ragweed)	2/3/42	X	7/25/49	None
Mrs. J.S.K. 21 years		2	Spring and fall hay fever 4 years	Pollenosis (grass and and ragweed)	2/3/48	X	9/3/49	None

CONCLUSION

This report is based on personal experience gathered over a period of fifteen years, presented in the hope that it will act as a guide in the treatment of allergies arising or pre-existing in the pregnant woman. Each patient must be tested thoroughly, evaluated properly from the clinical history, and treated, not with heroic doses but cautiously and wisely. The pregnant woman tolerates moderate doses well, and the pregnancy usually terminates happily. Specific pollen therapy is the method of choice, starting with preseasonal treatment given in gradually increasing doses, reaching a maximum before the season starts, continuing through the season at proper intervals (once weekly) and leading into the perennial

(Continued on Page 798)

KAPOSI'S VARICELLIFORM ERUPTION TREATED WITH AUREOMYCIN

CHARLES HYMAN, M.D., F.A.C.A.

Atlantic City, New Jersey

KAPOSI'S varicelliform eruption has had considerable notice in the literature. Many reports are available as to its incidence, its relative occurrence in infants and adults, and its etiological nature. The viral nature of the disease has been demonstrated by many observers. Hershey and Smith⁷ demonstrated vaccinia virus in these lesions. Lynch and Steves⁹ reported on the role of the virus of herpes simplex in producing the Kaposi syndrome. Other workers^{8,1,11} have demonstrated the same etiological agents. All reports stress the intractability of the disease, two to four weeks being the normal course in favorable cases. Barton and Brunsting² reported seventeen deaths among sixty-seven cases, with gangrene a frequent complication.

Finland⁶ et al reported success in the treatment of herpes zoster with Aureomycin. Baer and Miller,¹ Bereston and Carliner,³ and more recently Bookman⁵ have also reported similar success in the treatment of Kaposi's varicelliform eruption with Aureomycin. The following case is reported because of the dramatic response to this therapeutic agent.

CASE REPORT

S. H., a twenty-six-year-old white man, was first seen January 21, 1950, because of fever, generalized aching, and a mild coryza. Physical examination was negative except for the coryza, a temperature of 101.2°, and evidence of a longstanding neurodermatitis involving the entire head and neck, and to a lesser degree the arms, trunk and legs. Both eyes presented cataracts attributed to the extensive skin lesion.

The presenting illness was considered as an attack of gripe, and symptomatic therapy with coal tar products was instituted. The following day the temperature gradually rose to 103, and a few vesicles appeared on the upper lip and face. Three hundred thousand units of penicillin was given, and the next day the temperature dropped to 99°. Despite the decrease in the fever, rapid progression of the vesicular lesion took place, and in another twenty-four hours the ears, nose, face, lips, and upper chest (to near the nipple area) were covered with weeping serous lesions. These varied from 1 in point to pin head in size and became intensely irritating. The entire face, ears, neck, and nose were swollen. The patient complained of pain over the entire head and neck. Speech was extremely difficult, and all motions of the head were painful. The parotid, submaxillary, and cervical lymph glands were enlarged, tender, and painful. When the temperature rose to 101°, an additional 300,000 units of penicillin was administered. Throughout the following two days, January 24 and 25, the temperature remained at 103°. The eruption became more extensive although confined to the same areas. Both eyes were closed by edema of the lids. The conjunctivae were congested. Fifty thousand units of penicillin was given every three hours on January 25 for a twenty-four hour period, with no effect on either the lesion or the fever. A blood count on January 26 showed hemoglobin 13.5 gm (84 per cent), red blood cells 4,700,000, mean corpuscular

From the Department of Medicine, Atlantic City Hospital, Atlantic City, New Jersey.

KAPOSI'S VARICELIFORM ERUPTION—HYMAN

hemoglobin 28, white blood cells 6,200, polymorphonuclear cells 69 (nonfilamented 35, filamented 34), lymphocytes 29, monocytes 2. Urine examination was negative. Blood culture was also negative.

At this point a diagnosis of Kaposi's varicelliform eruption was made on the

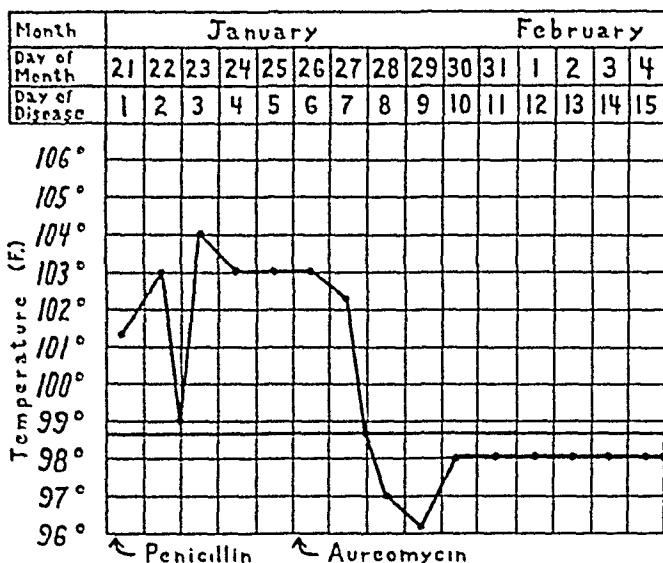


Fig. 1. Temperature chart.

basis of the probable viral nature of the initial febrile illness and the fact that the primary site of the acute skin lesion was a herpetic lesion below the alae nasi. The entire vesicular eruption seemed to extend from this focus. Since active penicillin therapy had failed and at this time it had become obvious that the lesion was of viral origin, a course of Aureomycin therapy was given according to the following schedule: 250 mg at 5 p.m., 6 p.m., 7 p.m., 8 p.m., then every six hours for six doses. Within less than twelve hours the temperature returned to normal and remained at a subnormal level until the patient became ambulant. The vesicles then began to dry and fall off. The generalized skin erythema gradually subsided. All the lymph glands returned to their normal size. Clearing of the lesions was aided by the application of warm boric acid compresses continuously. Numerous areas of skin came away leaving a raw bleeding surface, which healed readily after several days.

The clinical picture in the above case fulfilled the diagnostic criteria for Kaposi's varicelliform eruption.¹⁰ From the history it could be postulated that the point of entrance for the virus was on the upper lip, from secretions produced by the coryza. The initial lesion may have been herpetic. The usefulness of Aureomycin in virus diseases and its recent encouraging results in herpes zoster⁶ suggested a trial in this case.

Since this case was treated, a report has appeared by Bookman⁵ describing a similar dramatic response in a case of Kaposi's varicelliform eruption. He also notes a second case similarly treated with the same result. Bookman also refers to case reports by Baer and Miller,¹ and Bereston and Carliner,³ who have treated Kaposi's varicelliform eruption with Aureomycin.

KAPOSI'S VARICELLIFORM ERUPTION—HYMAN

SUMMARY

1. A case of Kaposi's varicelliform eruption is described.
2. Rapid disappearance of the skin lesions took place with Aureomycin therapy.
3. On the basis of this report and similar cases in the literature, further trial with this antibiotic is indicated.

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(Continued from Page 746)

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634 N. Grand Blvd. (3)

ACUTE ALLERGIC CONDITIONS OF THE ABDOMEN

A Clinical Report

F. B. SCHUTZBANK, M.D., F.A.C.A.

Tucson, Arizona

THE physician's ingenuity is often taxed in differentiating between an acute surgical and an acute medical condition of the abdomen. The diagnosis may be made easier in some cases if it is kept in mind that an acute attack of the digestive tract may be the manifestation of a food allergy. Such attacks may simulate a perforated ulcer, gall bladder or renal colic, intestinal obstruction, acute pancreatitis, appendicitis, and coronary or mesenteric thrombosis. For such acute allergic attacks I have used the term "acute allergic conditions of the abdomen." No doubt many emergencies which require surgery, and in which no pathological lesion is found, represent this condition. The writer has never seen a patient with an acute allergic condition of the digestive tract who has not suffered from other definitely allergic conditions, such as seasonal or perennial hay fever, asthma, urticaria, eczema, migraine, or colitis.

All of us have seen cases of chronic dyspepsia, hyperactivity of the bowel with excessive rumbling and gurgling, excessive gas formation, intermittent diarrhea or constipation, so-called nervous stomach and bowels, gastric neuroses, and colitis, that are often, in my opinion, mild food allergy cases. I am certain that many people suffer a long time with chronic digestive tract symptoms, frequently seeking medical aid, when all that would be necessary for relief would be the elimination of some allergenic food to which they are sensitive.

Occasionally, a hypersensitive individual unknowingly ingests an offending food or a larger than normal portion of an allergenic food, and a severe reaction occurs which is responsible for an acute attack of the digestive tract. The following case reports are illustrative:

Case 1.—An engineer, aged thirty-nine, over a period of years suffered acute attacks of excruciating upper abdominal pain associated with collapse, a state of shock and unconsciousness. He was hospitalized in various cities where at least a half a dozen examinations, including x-rays and electrocardiograms, were repeatedly negative. Diagnoses upon admission to a hospital varied from gall bladder and renal colic, perforated ulcer, acute pancreatitis, and coronary or mesenteric thrombosis. Usually, before a diagnosis was agreed upon, the patient recovered, and fortunately, surgery had never been done. Several times on discharge, he was told that he had no doubt passed a gall or kidney stone. Recovery always occurred in two or three days. During an observed attack he was in a state of shock and the liver was palpable and tender. Pain under the right ribs was excruciating. On the third day, there was a subicteric tinge of the sclerae although he was recovering rapidly.

On questioning the patient and his wife, it was learned that he had perennial and seasonal hay fever, chronic dyspepsia with much rumbling and gas in his bowels,

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pruritus ani and a long family history of allergy. After he had recovered he had another examination, including complete allergy testing. In addition to reaction to several pollens and other inhalants, he gave a 4-plus reaction to eggs and chocolate. It then became known that both the last two attacks occurred on a Monday morning about forty-five to sixty minutes after he had eaten four eggs for breakfast. On the preceding days, he had spent the Sundays in the country and had brought home fresh eggs. He said, "They were so good I ate four." Since eliminating eggs and chocolate from his diet, he has had no further acute attacks in several years and his dyspepsia has improved. The pruritus ani and perennial rhinitis cleared up completely. Ingestion of only one or occasionally two eggs always caused a recurrence of the latter symptoms, but that was the limit of his tolerance lest he get an acute attack.

Case 2.—A white man, aged fifty, became acutely and violently ill with very severe abdominal cramps and mid-abdominal pain within twenty minutes after eating a hotel dinner. He soon developed severe diarrhea with profuse watery evacuations. These symptoms lasted about six hours and were followed by vomiting with collapse and complete inactivity of the bowels. A clinical diagnosis of intestinal obstruction with ileus paralyticus, on the basis of a possible volvulus or intussusception, was made by the attending physician, and the patient was immediately hospitalized. He gave a history of having had a similar attack six months before at which time he was hospitalized for five days. Abdominal roentgenograms showed no evidence of obstruction.

Several physicians in consultation for an hour considered surgical interference. On questioning the patient, it was revealed that he had suffered from hay fever, asthma, urticaria, eczema, angioneurotic edema, colitis, and severe pruritus ani. However, he was symptom-free as long as he was on an absolute milk-free diet. He had seldom eaten away from home in over twenty years. Just prior to the last two attacks he had eaten out, and on investigation it was found that he had unknowingly eaten foods containing milk. With epinephrine, antihistaminic drugs, and intravenous fluids, he improved rapidly and was up after three days. Before the history of allergy was obtained, he was considered to have had an acute surgical condition of the abdomen.

Case 3.—A white woman, aged forty-five, gave a past history of hay fever, asthma, colitis and chronic dyspepsia or indigestion for twenty years or more. For several years she suffered from frequent acute attacks of severe upper abdominal pain and cramps with "formation of gas pockets" which often required hypodermic injections for relief. Examinations by various physicians were always negative. She had been diagnosed as a gall bladder case with gastritis, duodenitis and pancreatitis, colitis, and gastrointestinal neuroses. During several of her severe attacks surgery had been considered, but she had refused because no definite diagnosis could be made and because she always recovered within a day or two.

On testing, she was found to be sensitive to several pollens and inhalants; food tests proved unsatisfactory. After trial elimination diets, it was found that when she was on a strict milk-free diet, her dyspepsia and colitis cleared up and the acute episode subsided. On several occasions when she ingested milk, symptoms developed in a short time. The severity of the symptoms varied with the amount of milk she had taken.

Case 4.—A white woman, aged forty-five, presented a clinical picture similar to that of the first case, excepting that with acute symptoms of the digestive tract she was also asthmatic. She was known to have a long history of hay fever, asthma, and

symptoms of the digestive tract. Fish always caused an allergic reaction shortly after its ingestion. At the time I saw her for the acute attack in question, she had not eaten fish but there was a platter of fish on the table. Someone had taken a portion of fish, used the same serving spoon to take some mashed potatoes and had left the spoon in the dish. The patient had taken some potatoes with the same spoon and received enough fish protein to cause a very violent reaction which required epinephrine. This relieved the asthma as well as the abdominal pain. Knowing this patient, the diagnosis was not difficult, but her severe abdominal symptoms could easily have been mistaken for an acute surgical condition.

Case 5. A five-year-old girl had been taking oral pollen extract for treatment of hay fever. One night, after she had helped herself to several large spoonfuls of honey, she developed severe abdominal pain. With this history, epinephrine and Benadryl were administered, and she was relieved of all pain in about one hour. Next day, there were no after effects and she was perfectly well except for a stuffy and runny nose. The honey had, no doubt, contained enough pollen to cause an allergic reaction.

One patient, a fifty-five-year-old male, who at first was thought to have an acute allergic condition of the abdomen, was hospitalized and emergency abdominal roentgenograms were taken. Free air was present under the diaphragm, and, at operation, a perforated ulcer was found. No previous ulcer history could be obtained, but he was known to have been an allergy patient for many years.

Almost any organ of the body can be the shock tissue in an allergic reaction. In the first case, the shock tissue was the liver. An acute liver swelling may cause excruciating pain, as the inelastic hepatic capsule is quickly stretched by the acute allergic edema of the liver tissues. In such a case, there is a great deal of absorption of the offending protein, either completely or partially digested, into the portal circulation, and it is carried directly to the liver. Absorption of an incompletely digested or undigested allergenic substance is more likely to cause acute symptoms of the biliary tract in a previously sensitized liver. In such instances, there is the usual antigen-antibody reaction to account for the allergic condition. In this case, the patient had a tolerance for one or two eggs and suffered no more than the customary dyspeptic symptoms, as previously described. But when four eggs were ingested a more acute reaction occurred. Here, there was probably absorption of native egg protein, as well as an excessive amount of egg, due to the large quantity eaten.

In the second patient, the shock tissue was the intestinal tract. The direct contact of the bowel with the offending food caused a severe enough reaction to lead to symptoms of intestinal obstruction and ileus paralyticus. Here, there was probably a combination of smooth muscle spasm in the intestinal wall and an acute allergic edema of the mucosa.

Although acute allergies of the digestive tract are usually due to foods, they can be caused by ingestion of drugs, oral pollen extracts, and sometimes by parenteral injection of allergenic substances. In this type of

ALLERGIC CONDITIONS OF THE ABDOMEN—SCHUTZBANK

case, the tissues of the digestive tract have been previously sensitized to the offending allergens.

In the differential diagnosis of such cases as described, the history is most important. Nearly all cases will give a history of other allergic manifestations which may give the clue; therefore, to suspect an acute abdomen of being on an allergic basis, the physician must be allergy-conscious. No doubt the etiology of colic and acute symptoms of the digestive tract in children is frequently due to an allergy to food.

During an acute attack, these patients will usually have little fever, if any, even though they are violently ill. The second patient described had a temperature of 100.4° on the second day. The white count is usually within normal limits, or it may be low at first and moderately elevated later. There is usually little or no abdominal muscle spasticity present, although there may be moderate spasticity, but rarely if ever marked or board-like rigidity. An acute abdominal attack with absence of rigidity is strong evidence of an acute medical abdomen rather than an acute surgical abdomen. Other laboratory tests and roentgenograms will usually be negative; however, an eosinophilia may be present in the blood or bowel mucus.

Too much reliability cannot be placed on skin tests because food extracts do not react in a large percentage of the patients with food allergies. Elimination diets are much more satisfactory in determining the offending foods. In the cases herewith reported, the egg- and fish-sensitive patients gave good skin reactions, but neither of the two milk-sensitive patients gave positive skin tests.

It must be remembered that an allergic patient may have an acute abdominal condition due to the usual or common disorders which are in no way related to allergy. In some cases, when a definite diagnosis is not possible, surgery might necessarily be resorted to in order to be certain.

SUMMARY AND CONCLUSION

1. Food allergies may cause acute reactions of the digestive tract and may simulate a perforated ulcer, gall bladder or renal colic, acute pancreatitis, intestinal obstruction and ileus paralyticus, and coronary or mesenteric thrombosis. In such cases, the term "acute allergic conditions of the abdomen" has been used.
2. Five cases are reported as illustrations.
3. When the gastrointestinal tract or liver is the shock organ, an acute attack may be mistaken for an acute surgical abdomen.
4. In any acute abdominal condition, where the diagnosis is not clear, the physician should be allergy-conscious and should question the patient or family about a past history of allergy, as there will nearly always be other allergic manifestations, present or past, to give a clue.
5. In determining the offending foods, elimination diets are more satisfactory in most cases than skin tests.

(Continued on Page 798)

FOOD ALLERGY

A Base Diet

MILTON MILLMAN, M.D., F.A.C.A.
San Diego, California

MUCH confusion has existed in recent years as to the relative importance of food allergy. Skin testing for foods has fallen into disrepute in many circles. Elimination diets in the hands of many men have frequently failed. Thus an important phase of allergy loses its lustre because of therapeutic ineffectiveness.

The basis of detecting food allergy is to control the symptoms, then add foods which, if responsible for allergic symptoms, will produce a demonstrable clinical effect. The skin tests play an important part in suggesting what foods to omit initially and what foods to add later. A positive skin test in the presence of a corroborating history is of even greater significance. The skin tests must be interpreted in the light of the other findings in each case. In many of the simpler cases, however, no food tests may be necessary at all, sufficient information being obtained from the history, the basic or other planned diets by trial, and removal of common offenders.

BASIC DIET PRINCIPLE

A basic diet is not a liberal diet, but it should be as adequate as possible in all nutritional aspects. Occasionally the basic diet is not balanced, but this should be followed for as short an interval as possible, new foods being added one at a time, concentrating first on making the diet balanced nutritionally. This diet is planned from foods which are less common offenders and must be modified depending on the history and the elimination of skin-positive foods. If this gives a base line with freedom of symptoms, each new food should be added singly, twice a day if possible, and continued at least four days before it can be considered innocuous and new foods tried.

It must be remembered, in this connection, that one food may cause symptoms for four or five days and that no clinical symptoms may show at the initial servings of the food. A strict knowledge and control of the foods in the diet is essential. The method of preparation is vitally important. We frequently find patients who we believe are following the diet and eating the correct foods, but seasoning them with garlic, tomato, onion, pepper, bacon, and other ingestants.

The diet below is the one I use routinely in my practice. It has the following advantages:

1. The physician can have the diet printed in pads and kept in his desk.
2. One does not have to know many different types of diets, each of which has to be modified anyway.
3. It can be easily balanced nutritionally.

4. The printed list has several different choices of each item so that removal of certain foods is easily accomplished and new additions can be made as indicated.

5. For the initial diet, the physician can and must know each of the foods, as to the frequency of sensitization, nutritional value, methods of preparation, and what the skin test means for each food with his extracts and method of testing.

It is important to note that few patients get the diet as printed. It is modified for each patient depending on the history as obtained by questioning, food check lists, and diary, and when necessary, by skin tests.

THE BASE ALLERGY DIET

Breakfast

- Pineapple juice, apple or grapefruit
- Coffee
- Wheat or oat cereal or rice
- Cane sugar
- Bread and butter
- Evaporated milk diluted with 50 per cent water
- Rye Krisp

Dinner

- Lamb, steak, veal, or roast beef
- Carrots, beets, celery, peas, lettuce, asparagus
- Soup—made with above vegetables
- White potato or sweet potato
- Tea with evaporated milk if desired
- Bread and butter
- Cane sugar
- Evaporated milk diluted with 50 per cent water
- Rye Krisp

Supper

- Pineapple juice, apple or grapefruit
- Coffee or tea
- Carrots, beets, celery, peas, lettuce, asparagus
- Lamb, steak, veal, or roast beef
- Evaporated milk diluted with 50 per cent water
- Rye Krisp; bread and butter

Salt is allowed; Crisco used for cooking if butter is not allowed. No substitutions may be made without the consent of the doctor. A food eaten at one meal can be eaten at any other. No seasoning is allowed unless specifically recommended.

Apple and grapefruit are common allergens and are frequently omitted from the preliminary diet. Wheat is a very common allergen and is omitted if there is a question of wheat allergy. It can be omitted from the original trial diet and added in a short time to determine its clinical effect. Beef sometimes causes allergic symptoms, but in general beef, lamb, and veal work out satisfactorily. When wheat is allowed, bread can be included providing that it is egg-free.

Evaporated milk is a good milk for routine use, inasmuch as individuals

allergic to whole milk can frequently tolerate evaporated milk. Butter must be omitted if there is a tendency to milk allergy. Various cheeses can be added to the diet if there is no milk allergy, but different cheeses are made from the milk of several different animals, and this may have to be watched.

Carrots, celery, peas, and beets are potential allergens, but are satisfactory in many instances on the initial routine basic diet. Potatoes and coffee likewise are potential allergens and may have to be removed if an indication exists.

Asparagus, lettuce, and other foods may be substituted depending on the history, skin test, and the general picture.

Only one type of cereal is used initially. If wheat is to be included, wheat cereals can be allowed. In the absence of wheat, oat cereals or rice may be included. Rye Krisp is permitted if wheat is not included in the diet.

With this basic diet, modified as indicated above, many food allergy problems have been solved. After the base line is established, the new foods are added one at a time as previously outlined, leaving the suspicious foods—noted by history, skin test, and avoidance of common allergens—to the last. Vitamins are not added routinely to the initial diet since they too may act as allergenic agents. The multiple vitamins are added shortly after the base line is established or within one to two weeks after the initiation of the diet.

SUMMARY

1. A printed list of foods which can be easily modified into a basic diet has been presented.
2. A discussion of its clinical use has been outlined.
3. Emphasis has been made that there is no perfect elimination diet satisfactory for everyone, but that if the physician has at hand such a list as that described, he can modify it up or down easily as the case requires.

Medico-Dental Building

233 A Street

An item from our national clipping service reports that Jonathan Forman, M.D., F.A.C.A., immediate past president of The American College of Allergists, recently spoke on the subject "Hives" before a session of the Southern Medical Association in St. Louis.

Doctor Forman's new address is 5570 Riverside, R.F.D. No. 2, Worthington, Ohio.

Editorial

The opinions expressed by the writers of editorials in the ANNALS do not necessarily represent the group opinion of the Board or of the College.

SEVENTH ANNUAL CONGRESS

The final program of the Seventh Annual Congress of the College, as well as that of the three-day Graduate Instructional Course, appears in this issue. There will be no charge for registration for the scientific program, and all physicians interested in allergy are cordially invited to attend. Since, in addition to these features, there will be thirty-five technical exhibitors comprising the leading pharmaceutical houses and the manufacturers of products of interest to allergists, and scientific exhibits, particularly on ACTH, Pyromen, and bacterial allergy, together with sound pictures as a special attraction, a registration of at least one thousand is expected.

The short instructional course was arranged as a practical refresher course for the busy allergist and also in an effort to stimulate the young allergist to apply the most recent diagnostic procedures and methods of management. It was early discovered, when the College commenced its instructional courses, that the students interested in the practical application of their knowledge to help their patients lost interest when the course was devoted mainly to the fundamentals of immunology, immunochemistry, physiology, pathology, and so forth, because they could obtain this information from standard textbooks. They were not interested in a lofty lecture on investigative observations of many syndromes, infrequently encountered although undoubtedly mediated by immune mechanisms. The students are eager to learn a high quality of diagnosis and treatment which would aid them in their practice. Therefore, the framework of the instructional course this year consists of the methods of history-taking and skin testing, and practical lectures on pediatric allergy, the eczemas, hay fever, asthma, gastrointestinal allergy, food allergy, vernal conjunctivitis, and other allergies met with in the various domains of the body. The status of ACTH therapy will also be presented.

It is interesting that the practical courses are also attended by a number of certified young specialists well trained in their own specialty but not in allergy. They are becoming increasingly aware of the importance which human hypersensitivity plays in disease states.

The Program Committee purposely omitted lecturers on highly controversial subjects, who are sincere but overenthusiastic advocates of procedures which are still without sufficient evidence of their validity.

The Edgewater Beach Hotel is equipped to handle comfortably a large convention, and its isolation from the loop district has many advantages.

EDITORIAL

These short conventions are planned mainly for the exchange of ideas in the field of allergy and to promote cordial relations among its members, including some relaxation; they have never been planned as a vacation for the busy physician.

The scientific program will open with the general session on Monday morning. The remainder of this time, aside from the presidential and guest speakers' addresses and the business meeting, will be taken up with sections on psychosomatic, pediatric, otolarynologic, and dermatologic allergy. The final afternoon will be devoted entirely to a panel on rheumatism and arthritis.

Those who have not made reservations should do so at once, directly with the Edgewater Beach Hotel, Sheridan Road, Chicago, stating the exact time of arrival and departure and whether a single or double room is desired.

MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

(Continued from Page 764)

ferent kinds of fungi associated with ball moss as a substrate can probably best be explained by the peculiar nature of the tissues of the plant which would seem in part, at least, to be due to water-holding ability (hygroscopicity).¹

When the large amount of surface thus provided by each moss plant as a likely substrate for the growth of fungi in large numbers and of diverse kinds is considered—together with the fact that, being air-borne, these fungi may be potential respiratory allergens—it would seem, therefore, that in analyzing an environment for sources of fungi, the *Tillandsia* mosses constitute possible hazards for sensitive individuals.

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Progress in Allergy

ACTH AND CORTISONE IN THE MANAGEMENT OF THE HYPER- SENSITIVITIES, WITH PARTICULAR REFERENCE TO BRONCHIAL ASTHMA

A Review of Clinical and Laboratory Studies

MAURICE S. SEGAL, M.D., F.A.C.A., and J. AARON HERSCHFUS, M.D.

Boston, Massachusetts

THE advent of potent purified preparations of cortisone and pituitary adrenocorticotrophic hormone has revolutionized the management of a wide variety of chronic illnesses. Spectacular control of symptomatology and remissions has been described in a wide diversity of disease entities since the epoch discovery by Hench and his associates^{18,19} of the use of cortisone and ACTH in the treatment of rheumatoid arthritis and of cortisone in rheumatic fever. Recently Thorn and his associates^{44,45,46} in a comprehensive series of papers reviewed their laboratory and clinical observations, as well as those of other investigators, with ACTH and cortisone. Their discussion of these hormones included the preparation of ACTH and cortisone, the mechanism of action, metabolic effects, immunologic properties, toxicity and undesirable effects, and also clinical indications. They divided the disease entities which have been treated with ACTH and cortisone into three main groups: most useful, may be useful, and of questionable value. In addition, they listed the diseases in which these agents are of no value and may even be detrimental. Prominent in the first two groups were the hypersensitivities, namely, urticaria, serum sickness, exfoliative dermatitis, Loeffler's syndrome, status asthmaticus, and vasomotor rhinitis.

The limited (initial) supply, the prohibitive cost of these powerful therapeutic agents, and the impetus of Hench's work directed their earliest application to the management of a variety of collagen disorders: namely, rheumatoid arthritis, acute rheumatic fever, lupus erythematosus disseminatus, dermatomyositis, periarthritis nodosa, scleroderma, et cetera. Somewhat later their use in hypersensitivity states followed. The therapeutic results in the more common hypersensitivities have been found to be even more spectacular than those observed in the collagen disorders.

A series of encouraging preliminary reports describing the use of ACTH and cortisone in the asthmatic patient have appeared. Bordley et al^{3,4} wondered whether the dramatic responses to cortisone and ACTH observed in rheumatoid arthritis and rheumatic fever might not result from some change induced by these agents upon the mechanisms of hypersensitivity, inasmuch as Rich²⁹ had clearly shown that the basic anatomic lesions of the rheumatic diseases could be reproduced experimentally in animals by the induction of allergic reactions. They were impressed also by the striking and rapid improvement which followed the use of ACTH in a patient with exfoliative dermatitis from iodine.

In their preliminary reports^{3,4} they discussed the results of therapy with ACTH in four patients with lupus erythematosus disseminatus, seven patients with bronchial asthma, and two patients with acute (serum type) penicillin reactions. The clinical response in all of these patients was most favorable. The seven patients with bronchial asthma were of the severe chronic type; five were believed to be of the

Dr. Segal is Clinical Professor of Medicine, Tufts College Medical School, and director, Department of Inhalational Therapy, Boston City Hospital.

Dr. Herschfus is a research fellow in medicine, Tufts College Medical School.

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intrinsic type, and two of the type due to combined intrinsic and extrinsic factors. Their ages varied from twenty-six to sixty-three years, and the duration of the bronchial asthma from five to twenty-three years. The patients had been in severe distress for months and had obtained only partial and brief relief from established therapy. When ACTH therapy was started, all other medications (save placebos) were discontinued. Unequivocal benefit was noted in from four to forty-eight hours. The dosage schedules employed in this series appear to have been comparatively low. Twenty to one hundred milligrams daily in divided doses at six-hour intervals were administered. Therapy was continued from nine to twenty days. The total amount of ACTH given varied from 360 to 775 milligrams. All signs and symptoms disappeared in from one to eight days except in one patient, six months pregnant, who felt entirely relieved but in whom some rhonchi persisted. Spirometric tracings disclosed release from the relative obstruction to outflow at the time of symptomatic relief.

The authors described interesting changes in the para-nasal sinuses. There was rapid disappearance of edema and a change in color to bluish pink in those patients with pale edematous polypoid nasal membranes. The breathing space was greatly enlarged. The lymphoid tissue, when edematous, likewise assumed a normal color, and the crypts became more prominent. There was no gross change (shrinkage) in volume of the lymphoid tissue present. Two of the patients had polyps which completely obstructed the nose; the polypi began to shrink before the fifth day of treatment, and disappeared entirely in one patient and almost disappeared in the other. Polypi reappeared in one patient in twenty-three days, and in the other the remission lasted one month. Three patients with antral clouding by x-ray presented normal sinus x-rays after ACTH therapy. Similar changes to a less marked degree were observed by Rose³⁰ and Segal et al.³⁹

Rose et al.^{30,20} made a series of preliminary reports describing their observations on the effect of ACTH in one case of Loeffler's syndrome, one case of tropical eosinophilia, and six cases of bronchial asthma. The first case, a man of forty-four, had a classical Loeffler's syndrome with pulmonary infiltrations and an eosinophilia of 2865/cu mm before treatment. He was given 140 mg of ACTH in four divided doses over a four and a half hour period. The second case, a young Indian student, aged twenty-one, had typical changes in chest x-rays and marked eosinophilia. The total white count was 46,630 of which 39,130 (83.9 per cent) were eosinophils. He received 120 mg in two divided doses over a four and three-quarter hour period. A transient increase in total circulating leukocytes occurred in both cases. A virtual disappearance of eosinophils, from 2865/cu mm to 54/cu mm, was observed in ten hours in the patient with Loeffler's syndrome. The circulating eosinophils did not return to their pre-ACTH level over a subsequent two-year period of observation. A complete clinical and x-ray remission of the disease followed and has persisted. The well-known tendency for spontaneous remission in Loeffler's syndrome was appreciated by the authors. In the patient with tropical eosinophilia, however, although a decrease in total eosinophils (from 39,130/cu mm to 25,700/cu mm) occurred by the twelfth hour, it did not persist. The difference in the response of the eosinophil count to ACTH in these two disorders was not explained. The pulmonary infiltrations persisted, and the patient was then treated with mapharsen. A complete remission of symptoms followed this therapy. The duration of ACTH therapy may have been inadequate. Of further significance is the fact that the authors were able to confirm their previous observations that no correlation existed between blood histamine and fluctuations of eosinophils in studies on these two patients. Of greater significance was the fact that the histamine values were all within normal range, despite the marked eosinophilia and subsequent eosinopenia. This appears to corroborate that the eosinophil in man is not responsible for carrying histamine.

Rose and his associates³⁶ had previously studied the metabolism of histamine and

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its specific enzyme histaminase in adrenalectomized rats, and in normal, asthmatic, and pregnant patients. Encouraged by their recent observations of the relationship of asthma to Loeffler's syndrome which is benefited by ACTH, and the demonstration by Thorn et al¹³ of the eosinopenic effect of ACTH in humans with intact adrenals, they then extended their preliminary observations with ACTH to asthmatic subjects.^{30,35,36} They treated six patients with severe intractable bronchial asthma of three to eight years' duration with ACTH.^{30,35} One patient had in addition rheumatoid arthritis and another had periarthritis nodosa. Extensive metabolic studies were carried out while the patients were observed under conditions of controlled caloric and electrolyte intakes. After the sixth hospital day they were given intramuscular injections of sterile water, at six-hour intervals. ACTH was substituted for the latter on the tenth hospital day, on the same time schedule. The first two patients received 150 mg daily for two days and then 100 mg for two more days, making a total of 500 mg over the four-day period. The next four patients received 100 mg daily for three days, 75 mg daily for two days, and 25 mg on the sixth day, making a total of 475 mg. The patients received non-specific medication such as epinephrine or aminophyllin when necessary.

The signs and symptoms of rheumatoid arthritis and periarthritis nodosa in two of the patients were greatly improved with a complete remission of the bronchial asthma. The vital capacity and maximum breathing capacity improved in all of the patients. There was shrinkage but no complete regression of the thickened polypoid nasal and antral mucous membranes. Unfortunately, the longest remission observed was one month, with return of symptomatology to its former severity by the end of the sixth week. There was complete remission in four patients within forty-eight hours, and in two patients there was considerable improvement but no complete remission.

Rose³¹ later discussed his experiences in ten patients with manifestations of hypersensitivity, including urticaria, allergic rhinitis, asthma, periarthritis nodosa, and acute disseminated lupus erythematosus. Satisfactory clinical improvement was noted in six patients. The longest remission noted was six weeks.

Randolph and Rollins^{26,27} anticipated usefulness of ACTH in allergic states because of the relationship of the pituitary-adrenal axis to the immune reaction, and the eosinopenic effect of ACTH. They discussed their experiences with ACTH in thirteen patients with allergic syndromes. Ten of the eleven asthmatic patients obtained considerable relief (50 per cent to 100 per cent range) for one week to five months following a single brief course of therapy. The dose schedule was 25 mg every six hours. The total dosage ranged from 125 to 325 mg (lower than that employed by Rose et al and Bordley et al). Clinical improvement was noted four to six hours after the initial 25 mg dose in three of their first four patients. These three remained markedly improved for twenty-one days after treatment was stopped. Mild residual asthmatic symptoms, which did not require medication after the first day of treatment, persisted. In each patient, however, there was a gradual return of asthma during the fourth week requiring the use of symptomatic measures for relief. The first three patients were then re-hospitalized because of bronchial asthma of the former severity, and a second identical course of ACTH was followed by similar improvement.

Randolph and Rollins found ACTH least effective in patients with pulmonary emphysema and scarring from pleurisy and empyema. They noted striking improvement in the reactivity of several patients sensitized to food allergens (oral and inhalant). Three patients with asthma were known to be clinically sensitive to several food allergens capable of producing asthma. Deliberate feeding tests repeated during or immediately after stopping ACTH therapy produced but transient accentuation of symptoms or showed complete tolerance of the food allergen. One pa-

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tient with atopic dermatitis, reproducible by wheat ingestion and curable by wheat avoidance, showed a striking improvement which lasted for five days after receiving 350 mg of ACTH administered over a fifty-hour period. During the week following ACTH therapy, the dermatitis recurred to a greater degree of severity than previously observed. Another patient with a similar atopic dermatitis, highly sensitive to corn ingestion, was successfully treated with a total of 225 mg of ACTH administered over a three-day period. Improvement continued in spite of the continual ingestion of corn products during ACTH treatment. Following the course of ACTH therapy, corn was omitted and this improvement was maintained for ten days. Unfortunately, as with the first patient, the extensive dermatitis reverted to a greater degree of involvement than existed prior to these observations. A third patient, known to be violently sensitive to wheat, developed cramps and diarrhea following its ingestion. Prior to therapy with ACTH, she was ill for three weeks with colitis. She was given a course of ACTH, receiving a total dosage of 325 mg over a period of eighty hours. She became symptom-free on the third treatment day and was able to tolerate a meal of wheat gruel one day after cessation of ACTH therapy. She subsequently tolerated a general diet including wheat and other food allergens for a period of twelve days, and she gained weight. Abdominal cramps and diarrhea then recurred but were controlled for another week by excluding wheat from the diet. A fourth patient presenting a violent reaction (headaches, rhinitis, and gastrointestinal reactions) to the inhalation of cooking pork had relief of symptoms after receiving 33 mg of ACTH. The authors treated three additional pork-sensitive patients successfully with ACTH. Conn⁸ in discussing these observations, briefly mentioned twice relieving food urticaria in a boy with 25 mg doses of ACTH.

The authors also reported striking amelioration of ragweed hay fever symptoms in four patients and complete protection for the remainder of the season in three of these patients with ACTH. The dosage ranged from a total of 125 to 250 mg administered over a twenty-four- to fifty-four-hour period, between August 31 and September 11, 1949.

Segal et al^{38,39} administered twenty-seven courses of ACTH therapy to twenty patients with severe chronic bronchial asthma over an eight months' period (January through August, 1950). There were fourteen females and six males in this series. The patients' ages varied from fifteen to seventy-two. They were all seriously ill with a wide variety of associated and related defects: hay fever, atopic eczema (aureomycin), nasal polyps, sinusitis, severe bronchitis, various degrees of emphysema, cor pulmonale, hypertension, cerebral arteriosclerosis, and diabetes mellitus. In general, higher total doses than previously reported were employed. The initial dose of 40 mg was repeated in six hours. It was followed by 20 mg every six hours until lasting benefit had been observed for two days. If improvement continued, the time interval was then increased to every eight hours for one to two days or longer. Usually after the fourth day of therapy the time interval was further increased to every twelve hours until the time of discharge. The total doses of a single course of therapy varied from 240 mg to 900 mg and the duration of therapy from two and a half days through nineteen days.

The immediate therapeutic effect in the twenty-seven courses administered was as follows: failure, two; fair, four; good, three; and excellent, eighteen. The continued therapeutic effects was as follows: failure, three; fair, eight; good, ten; and excellent, six. Unfortunately the period of remission was generally short. Repeated intensive courses of therapy were frequently found necessary and appeared more effective than attempts at maintenance therapy. Failure to respond to the same degree was noted sometimes after the second course of therapy. The authors cautioned that repeat courses of therapy should not be employed too freely, inasmuch as the nature of the repeated remission and the effects of repeated hormonal over-stimulation might not be free of hazard. Clinical and postmortem evidence was

presented that the possible mechanism of death in bronchial asthma may be due to failure in the homeostatic mechanism (the hypothalamus-pituitary-adrenal axis) to provide an adequate level of ACTH for the secretion of sufficient adrenocorticoids. The vigorous use of ACTH ("therapeutic adaptation") in this type of patient at such a critical period may prevent death by compensating for this imbalance.

In addition to the above preliminary reports, several other case reports have appeared. Kanee et al²¹ administered ACTH to a fourteen months' infant who had had eczema since the age of three weeks and asthma since the age of twelve weeks. Ten mg was administered every six hours. Improvement of the eczema was noted within twenty-four hours and complete clearance in forty-eight hours. The clinical remission was still evident eight weeks after cessation of therapy.

Elkinton et al^{10,11} in their study of the effects of ACTH therapy included a five-year-old boy with status asthmaticus who showed remarkable improvement. They observed the development of resistance to ACTH in two patients. One patient with acute rheumatoid arthritis obtained less relief from the drug as time went on, though the dose was steadily increased until its use had to be discontinued because of the appearance of Cushing's syndrome. Another patient who was being treated for lupus erythematosus disseminatus, after having responded to ACTH initially, had recurrence and progression of symptoms, despite 200 mg daily. This patient died. Serologic studies indicated that some type of antibody to the adrenocortical preparation was present.

Forsham,¹² in an interesting discussion of various types of sensitivity to ACTH, comments on the appearance of hives, anaphylactoid reactions, and the decreasing activity of similar doses in the same patients. Preliminary observations in a case demonstrating diminished effectiveness of the same daily dose showed the presence of ACTH neutralizing antibodies. Variability of lot potency and changes in the responsiveness of the adrenal cortices were considered and ruled out. Furthermore, he noted less resistance to the hormone developing with continued ACTH administration than when the course of treatment was interrupted for one to two weeks.

Thorn et al,^{11,45,46} in their review articles previously referred to, treated three patients with severe chronic bronchial asthma, employing doses of 10 mg of ACTH every six hours. All the patients showed marked improvement for five to seven days after the cessation of therapy. A second patient on a similar schedule had no recurrence of asthma for one month after cessation of ACTH. The authors concluded that doses of 10 mg every six hours were capable of alleviating the asthmatic symptoms in the majority of the patients but that improvement may not be maintained after therapy has stopped. They considered that ACTH was the drug of choice in cases which had become irresponsive to the usual therapeutic measures and furthermore that restoration of the therapeutic effectiveness of other more common agents would be noted with the ensuing remission.

These authors also treated one patient with severe, persistent vasomotor rhinitis of two years' duration with ACTH, employing 10 to 12 mg every six hours for ten days. Previously the usual antihistaminic agents and hyposensitization had been only slightly effective. Improvement in nasal patency and rhinorrhea was observed within twenty-four hours after starting ACTH. The signs and symptoms of allergic rhinitis disappeared after ninety-six hours. Improvement has persisted for three months to date.

Samter³⁷ treated six patients suffering from bronchial asthma with ACTH. Four patients showed satisfactory improvement and two patients significant improvement. Details of management and clinical response were not given. The improvement noted was described as proportional to the metabolic and hematologic changes. If a patient failed to show an increase in the urinary excretion of 17-ketosteroids and 11-oxygenated corticosteroids, and a decrease in the number of circulating eosinophils, he also failed to show clinical improvement. Changes in excretion of 11-oxygenated cortico-

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roids and in breathing reserve as effected by ACTH are shown to be similar under the influence of fever and an unknown stimulus.

Astwood and his associates² prepared three different, therapeutically active preparations of corticotrophin (ACTH) and reported their observations on forty-two patients treated for a variety of diseases. In this preliminary report they treated five patients with bronchial asthma. The patients' ages ranged from nine months through sixty-seven years. The adult patients were given 20 mg of preparation A at six- to 8-hour intervals for five to twelve days. The infant was relieved by 10 mg of preparation B every six hours but not by 5 mg of preparation A every twelve hours. Convulsions developed while using the large dose and did not return with the lower dose. Three patients who had been in a state of constant asthma for six to eight months were promptly and completely relieved of all signs and symptoms of bronchial asthma. A man, aged forty-four, suffering from periodic attacks of bronchial asthma, was moderately benefited. A woman, aged forty-nine, with mild asthma improved, but accompanying rhinitis and sinusitis persisted. A sixth patient, aged thirty-five, with allergic rhinitis received 80 mg daily of preparation A for three days and had a complete remission which persisted as long as followed (time not mentioned).

Brown⁵ recently made a concise review of selected papers dealing with ACTH, its pharmaco-physiology in rats and humans, and the clinical results obtained by several investigators in a variety of disorders. He concluded that in ACTH we may find a powerful remissive agent for the acute hypersensitivities (penicillin and drug reactions) and a temporary remissive agent for the more chronic disorders (hay fever and bronchial asthma). Brown wisely encourages the continued search for and elimination of the basic sensitivities and urges that the internist-allergist become more familiar with the metabolic and endocrine relationships involved with ACTH therapy.

Burrage⁶ in a recent, succinct review of the progress in allergy cautions that despite the dramatic temporary cessation of symptoms observed with ACTH in allergic diseases, one should not hastily conclude that the problem of allergy is about to be solved. The fundamental process by which ACTH and cortisone affects these diseases must first be determined.

* * *

Observations on the effect of cortisone on bronchial asthma and hay fever have been very limited. Randolph and Rollins²⁸ treated five patients with bronchial asthma with cortisone. In four patients they made comparative studies of cortisone and ACTH therapy. They found cortisone partially effective in relieving the symptoms of intractable asthma but, in the doses employed, less effective than ACTH. Both cortisone and ACTH caused the same hematologic changes. One patient obtained no relief with cortisone but had a satisfactory response from cortisone with supplemental vitamin C intravenously. Another patient on vitamin C orally relapsed after several days. When given cortisone with vitamin C, he exhibited a more complete and sustained clinical response. Segal et al³⁰ were unable to potentiate or prolong the effects of ACTH with intravenous cavitamic acid (4 grams daily for as long as five days in several patients).

Carryer et al⁷ observed the effect of cortisone under controlled conditions in three patients suffering from hay fever and seasonal asthma due to ragweed pollen. The patients received 100 mg of cortisone or 100 mg of cholesterol crystals (control) daily for four weeks. The results with the cortisone were considered beneficial. Each patient experienced prompt relief. The symptoms of bronchial asthma were relieved more quickly than the hay fever symptoms. Only mild, transitory symptoms persisted after three days of cortisone. Symptoms recurred shortly after cessation of treatment.

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In another study (limited to three patients) cortisone did not prove as effective as ACTH in controlling the asthmatic state or in inducing an adequate eosinopenia.³⁹ One patient received 300 mg of cortisone over a three and a half-day period, immediately following an initial unsuccessful remissive attempt with ACTH. There was no clinical improvement. The previously obtained eosinopenia could not be maintained. A second patient received a total of 510 mg of ACTH during eight days with complete amelioration of respiratory symptoms except for exertional dyspnea, and with considerable improvement in his associated rheumatoid arthritis. Because of insufficient supply of ACTH, he was then given cortisone, 150 mg in three days. This was ineffective in controlling either his respiratory symptoms or his joint manifestations. As with the first patient, the eosinopenia could not be maintained. A third patient was given cortisone initially in an attempt to alleviate severe status asthmaticus. Thirty mg intramuscularly were administered every eight hours for six doses (180 mg) with no clinical improvement or drop in the control eosinophil level. ACTH was then substituted for cortisone. He received 420 mg over six and a half days with an excellent remission and eosinopenia. This remission lasted for six weeks. During this period he was given small (25 mg) weekly doses in an attempt at maintenance therapy. ACTH was abandoned after two nearly fatal anaphylactoid reactions. About seven weeks later, the patient developed a most severe degree of status asthmaticus and cor pulmonale requiring hospitalization. He was refractory to all medication. An intensive course of cortisone was begun and he received a total of 600 mg until his death on the second hospital day.

One cannot help speculating whether ACTH, which was not administered at this time because of the previous toxic reactions, might not have been effective. The studies by Forsham et al¹⁵ on the functional state of the adrenal cortex during and following ACTH and cortisone therapy revealed that cortisone therapy (100-200 mg daily) suppressed both adrenal cortical activity and the response to ACTH for up to ten days after therapy. When ACTH (100 mg daily) was added to the cortisone therapy, an additive effect rather than suppression of the 17-ketosteroids was observed. When only 40 mg of ACTH was used daily, 100 mg of cortisone a day failed to show a rise in 17-ketosteroid excretion. This suggested to the authors that cortisone acts through pituitary ACTH inhibition, rather than through any inhibitory effect on the adrenal cortex itself.

STUDIES CONCERNING THE MODE OF ACTION OF ACTH AND THE NATURE OF THE IMMUNE REACTION.

A masterful study in rabbits by Harris and De Groot¹⁷ postulated a neurohumoral mechanism (adrenergic in nature) by which stimulating influences from the hypothalamus may be transmitted to the anterior pituitary gland, with a resultant release of ACTH. This phenomenon of activating the pituitary through a peripheral sensory stimulus was applied in an extremely interesting study by Hume and Wittenstein²³ in a series of operations on dogs. The eosinopenic response to surgical stress, before and after making electrolytic lesions in the hypothalamus, was observed. They concluded that the following factors were significant in the release of ACTH from the anterior pituitary following stress: (1) An intact hypothalamus is essential. (2) Lesions in the hypothalamus abolish or decrease the response even in the presence of an intact pituitary-adrenal cortex. (3) The hypothalamic control of the pituitary seems to be mediated by means of a hormonal mechanism, inasmuch as severing of the nervous and vascular connections between the intact hypothalamus and pituitary did not abolish the eosinopenic response to stress. (4) Complete sympathectomy did not alter the response; so that neither epinephrine nor sympathetic fibres to the pituitary are essential to pituitary release of ACTH following stress.

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A marked release of ACTH from the pituitary followed remote control stimulation of the hypothalamus in a sympathectomized animal, and finally (5) preliminary work with extracts of beef hypothalamus seemed to indicate the presence of a special pituitary-stimulating hormonal substance.

Rose and his associates³⁰ had previously demonstrated in rats the direct relationship between the adrenal cortex to the metabolism of histamine and its specific enzyme histaminase. The tissue and blood histamine was markedly increased and the mechanism for the destruction of histamine was impaired following adrenalectomy. They were able to fully restore these changes by the administration of cortin but not by desoxycorticosteron.³² Selye⁴⁰ more recently has shown that the administration of DOCA intensifies the anaphylactoid state, whereas cortisone or ACTH protects. Cortisone and ACTH also protected sensitized adrenalectomized rats to the lethal anaphylactic reactions of egg white injections.

Spontaneous remission of bronchial asthma during pregnancy has been observed by most investigators. Venning⁴⁷ reported an increase of urinary glycocorticoids, and Ahlmark¹ found an increase in plasma histaminase during pregnancy. Rose et al³⁴ had previously shown that compared to the normal pregnant woman, the level of plasma histaminase is impaired in the asthmatic who fails to have a remission during pregnancy. They³³ also found a higher histamine content in the shock organs (lung, skin, or mucous membranes from nasal passages and antra) in allergic patients as compared with those from normals. Histamine and histidine^{30,35,36} excretion in the urine was measured before and after ACTH administration, and nearly all the patients demonstrated a marked increase in the histidine output with levels sometimes reaching as high as those seen in pregnancy. This was noted within twenty-four hours after the administration of ACTH, and the values promptly returned to normal after withdrawal of ACTH. An early report³⁰ on six asthmatic patients indicates an excess of histamine in the urine before treatment. Urine histamine disappeared in five but increased in the sixth patient, who did not have a complete remission. The urinary 17-ketosteroids were increased in five patients, but failed to rise in the sixth patient, in whom there was also a delay in urine histamine decrease, as well as a failure of eosinopenia.

The reader is referred to the masterful presentation by White⁴⁸ summarizing the experimental evidence for the role of the adrenals in the immune mechanism and the role of the pituitary-adrenal axis in the allergic state. White discussed the role of the reticulo-endothelial cells involved in the immune mechanism. He cited evidence of lymphocytic dissolution following increased pituitary-adrenocortical secretion and evidence that in the immunized animal one of the constituents of lymphocytes is antibody globulin. Additional evidence was presented that the adrenals are involved in the maintenance of the tonus of the ground substance of the mesenchyme. Tissue permeability (intradermal spreading) was decreased by injections of adrenocortical extracts. Implications of the role of the adrenals in resistance against invasive organisms and toxins are thus apparent.

The possible implication of the inhibition of mesenchymal permeability, as described by White, as a *modus operandi* of ACTH therapy in bronchial asthma was also referred to by Samter in the same journal issue.³⁷ The latter discussed in an engaging manner a series of facts and speculations concerning the physiologic mechanism involved in allergic manifestations and possible mechanism of ACTH in the allergic state. He raised the question as to the possible relationship between tissue permeability and ACTH. He was able to demonstrate protection with ACTH against the bronchoconstrictor effects of histamine aerosols (number of patients not mentioned). Similar protection has been noted by Rose et al³⁵ and Segal et al.³⁹ Samter assumed from this observation that the permeability of the (connective tissue) barrier had changed with ACTH therapy. On the basis of the evidence

presented, he further suggested that ACTH, through the release of corticosteroids from the adrenals, alters the mesenchyme of the bronchial shock tissue, rendering it less vulnerable to specific and nonspecific agents. The similarity in action in the allergic state between fever (real and artificial), ACTH and cortisone also suggests a more fundamental homeostatic mechanism rather than drug-like action. Further confirmation of this point of view may be found in the observations by Herschfus et al,²¹ wherein they were unable to demonstrate any significant antihistaminic or anticholinergic properties with single large doses of ACTH in the asthmatic subject. The repetitious eosinopenia induced by typhoid fever in a series of patients with bronchial asthma, as striking as that observed with ACTH, would appear to suggest a similarity in action between ACTH and fever.²² Promised investigation by Samter of other factors that determine the shock organ in the allergic patient, independent of pituitary-adrenal regulations, will be eagerly awaited.

The ability of ACTH or cortisone to modify antibody production was tested by Mirick²³ in twelve patients treated for bronchial asthma or other related diseases. The patients were vaccinated with pneumococcal polysaccharides, and serum was obtained at several-day intervals for several weeks. Antibody titer appeared promptly and in as high a titer in the eight patients who were treated with ACTH and in the four who were treated with cortisone as in the controls. The degree of induced skin sensitivity to pneumococcal polysaccharides was depressed in some patients during treatment. A consistent drop in the gamma globulin of the sera was observed in all but one of the treated patients, even though specific antibody titer against the pneumococcus was increasing all the time.

Forsham¹¹ mentioned that in four patients with lupus erythematosus disseminatus, an elevated gamma globulin was found which was markedly depressed by ACTH administration. In the same discussion an interesting curve drawn from one of these patients reveals a profound fall of gamma globulins when ACTH becomes effective with a definite rebound after cessation of therapy. A remarkable, constant inverse relationship of the complement titer to the gamma-globulin concentration was observed in all of these cases. Finland et al¹³ in an important contribution described the appearance of specific (pneumococcal type 8) agglutinins at the usual time in a patient with pneumococcal pneumonia successfully treated with ACTH.

Soffer et al⁴² attempted to block the Schwartzman reaction in rabbits with ACTH. ACTH did not influence the phenomenon when it was injected before the preparatory intradermal sensitization. However, when administered before the provocative intravenous injection, the Schwartzman phenomenon was completely inhibited in eight of the ten rabbits tested. The control groups showed a high incidence of reaction, and surgical pituitrin failed to inhibit the reaction.

Finally, numerous studies have appeared, attempting to shed some light on the immune mechanism and the inter-relationship of the hypothalamus-pituitary-adrenal axis in allergy by noting the effect of ACTH on skin testing, passive transfer studies, histamine metabolism, and protection against the bronchoconstrictor effects of histamine.

No consistent changes were observed in skin testing of the direct type in the earliest reports on ACTH therapy in the hypersensitivities. Bordley et al¹ reported a definite diminution in skin sensitivity to inhalant and bacterial antigens in one patient. The responses returned to their original levels in three weeks. Similar changes were not observed in skin tests of the direct type^{30,39} and also in passive transfer tests^{39,49} in other series of treated patients. On the other hand, Favour et al¹² have demonstrated that under the action of ACTH, the hypersensitivity phase of the reaction to tuberculin (delayed type) may be abolished. Guinea pigs sensitized to tuberculin showed disappearance of the tuberculin skin reaction while on ACTH.

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Following discontinuance of ACTH, it reappeared. Suitable controls all showed a good tuberculin reaction. Complete correlation was obtained by the use of a lympho-lysis test, in which lymphocytes from tuberculin-sensitized guinea pigs were lysed by adding tuberculin *in vitro*. The lymphocytes were lysed before and after ACTH, but not during ACTH administration. The hazards of such a change in hypersensitivity in the treatment of human tuberculosis remain to be determined.

Zeller et al¹⁹ made a detailed gross and histologic study of scratch and intradermal tests on two ragweed-sensitive patients successfully treated with ACTH. The reactions to scratch and intradermal tests and successful passive transfer studies were not altered after ACTH therapy. A histologic study of the allergic wheal revealed eosinophilia in the inflammatory exudate as the most constant finding. Following the blood eosinopenia induced by ACTH, the wheal eosinophilia is reduced in the treated patient, but the latter phenomenon was not transmitted to the passive transfer recipients. From one hay fever patient with ragweed whealing, a biopsy taken after epinephrine showed a drop in tissue eosinophilia. Antihistaminics, orally or locally, inhibited ragweed or histamine whealing, but ACTH failed. They concluded that ACTH alters the hypersensitivity state of the clinical shock organ without influencing gross skin effects, whereas the antihistaminics alter both.

Bordley et al⁴ tested four of their treated patients for sensitivity to histamine. All responded normally to intracutaneous histamine and likewise to intracutaneous curare both locally and by increased gastric flow of free HCl. They concluded that these tissues at least can produce histamine (or histamine-like substances) and react to it in the normal fashion while the patient is receiving ACTH.

Herschfus et al²¹ demonstrated that single large doses of ACTH did not prevent histamine- or methacholine-induced asthma in asthmatic subjects, as has repeatedly been noted with adrenergic or histaminolytic agents and aminophyllin. On the other hand, the abnormal sensitivity of the asthmatic patient to injected histamine was lessened or abolished by treatment with ACTH (repeated injections).³⁹ Similar studies with ACTH in induced asthma were carried out by Curry et al.⁹ Significant protection against the action of histamine and methacholine was not achieved with single doses of 50 to 100 mg of ACTH. These studies would indicate that ACTH probably does not relieve bronchial asthma through an antihistaminic or anticholinergic action.

Rose et al^{30,35} demonstrated that the ability of histamine or methacholine aerosols to produce dyspnea with bronchoconstriction was blocked in four patients by ACTH therapy. One of these patients also reacted less to the effects of aerolized grass pollens. We observed a similar marked improvement to the bronchoconstrictor effects of dog dander in one of our ACTH-treated patients.³⁹ Nevertheless, this patient did not derive satisfactory clinical relief from ACTH and cortisone therapy, nor did ACTH protect her against the effects of histamine intravenously.

Friedlaender and Friedlaender¹⁶ confirm the inability of ACTH to alter histamine and skin testing whealing in humans, and they were unable to protect guinea pigs against histamine and mecholyl-induced bronchospasm by single or multiple injections of ACTH.

The explanation for the variability in blocking by ACTH of the effects of a variety of stressors (histamine and allergens) at different target sites (skin and respiratory tract) is not apparent. However, these studies appear to demonstrate the lack of direct antihistaminic and anticholinergic properties as well as the lack of drug-like action of ACTH itself.^{4,9,16,21,30,37,49}

This review would be incomplete without reference to the splendid contributions by Hans Selye⁴¹ and the progressive development of his concept of the response of the body to stress, the general adaptation syndrome (G-A-S). The human

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being is able to withstand a wide variety of acute environmental stresses such as hypoxia, trauma, infection, hemorrhage, burns, fear, anger, anaphylaxis, histamine release, et cetera, by a complicated neurohumoral adaptive mechanism. The response to the stresses and strains of life are usually met with adequate adaptive responses (G-A-S) in which corticotrophin production plays an important part. Stress acts through the G-A-S, the latter developing in three stages: the alarm reaction (*shock and counter-shock*), the stage of resistance, and the stage of exhaustion. Adaptability and resistance to stress are fundamental prerequisites for life. Diseases of adaptation may follow in the wake of maladaptation (hypo-, hyper-, or dys-adaptation).

Selye's concepts attempt to explain how the G-A-S response may lead to a variety of unrelated diseases which are amenable to adrenocorticotropic hormones. The evidence is accumulating that bronchial asthma should be regarded as one of the diseases of adaptation (hypo-adaptation)—a derailment of the G-A-S. Selye gives evidence that the anti-asthmatic effect of the gluco-corticoids and of adrenergic substances suggests that the endogenous discharge of adrenal hormones may be a normal defense mechanism against the allergic response to stimuli. An adequately functioning hypothalamus-pituitary-adrenal axis is necessary for continued adaptation.

SUMMARY

The adrenocorticosteroids appear capable of intervening in the acute and chronic manifestations of hypersensitivity of body cells to bacterial and non-bacterial substances. They appear to inhibit the altered reactions of cells, probably at the mesenchymal level, rather than inhibit any of the direct toxic effects of the sensitizing agents themselves. Therapeutic benefit is achieved by creating a state of hormonal excess. "Therapeutic adaptation" for a state of hypo-adaptation (Selye) is thus possible with these agents. The exact mechanism of this action is still not understood.

The goal of all therapy in the patient with serious bronchial asthma is the production of a prolonged remission. Frequently, when such a remission occurs, one is unable to explain its genesis. Just as often one cannot bring about a second remissive episode employing the same procedure. ACTH apparently offers a way to cause such a remission more consistently than by any other therapeutic regimen.

However, improvement with ACTH frequently may be maintained for but a short period; prolonged administration is not feasible; there is some evidence that in relapse the symptoms of some types of hypersensitivity may recur with greater severity than before; and finally, repeated stimulation of the hypothalamus-pituitary-adrenal axis may not be desirable. To what extent undesirable physiologic and toxic effects which follow in the wake of ACTH and cortisone will limit their usefulness in the management of the more chronic allergic disorders remains to be revealed.

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(Continued from Page 773)

method (found best) once in two weeks. In addition, some patients will require small doses of a tried and established antihistaminic drug (Pyribenzamine 25 mg) for more complete relief. Attention must also be given to inhalant antigens, and desensitization must be carried out where indicated. All the cases reported here were delivered by various local obstetricians and experienced no flare-ups or complications.

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ACUTE ALLERGIC CONDITIONS OF THE ABDOMEN

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6. In some cases the administration of epinephrine and antihistaminic drugs will serve as a therapeutic as well as a diagnostic measure.
7. It must be remembered that even severe food allergy patients can have an acute abdominal condition from the more common non-allergic causes. All patients with acute abdominal symptoms must be studied carefully, and in some cases surgery may have to be done to be on the safe side.

4065 East Cooper Street

News Items

SYMPOSIUM ON ALLERGY

Wayne University College of Medicine and the Allergy Clinic of Detroit Receiving Hospital held a Symposium on Modern Concepts of Allergic Diseases at the Auditorium, College of Medicine, Wayne University, Detroit, on November 29. Jack Rom, M.D., F.A.C.A., Instructor in Clinical Medicine, acted as chairman. The following program was presented:

- Immunologic Aspects of Allergic Disease—recent progress and present status
Dr. SIDNEY FRIEDELAENDER, F.A.C.A., Instructor in Clinical Medicine
- Pharmacologic Aspects of Allergic Diseases
Dr. VICTOR A. DRILL, Professor of Pharmacology
- Pathology of Allergic Disease
Dr. OSBORNE A. BRINES, Professor of Pathology
- Internal Medicine and Allergy—recent progress, the collagen diseases
Dr. SAMUEL JACOBSON, Assistant Professor of Clinical Medicine
- Allergy and the Cardiovascular System
Dr. JACK ROM, F.A.C.A., Instructor in Clinical Medicine
- Gastrointestinal Allergy
Dr. HOMER HOWES, Instructor in Clinical Medicine
- Neurological Aspects of Allergy
Dr. GABRIEL STEINER, Professor of Neuropathology
- Psychiatric Aspects of Allergy
Dr. JAMES C. MOLONEY, Associate Professor of Psychiatry
- Allergic Dermatoses
Dr. LOREN W. SHAFFER, Professor of Dermatology
- Ocular Allergy
Dr. ALBERT D. RUEDEMANN, Professor of Ophthalmology
- The Management of Allergic Problems in the Surgical Patient
Dr. ALEX S. FRIEDELAENDER, F.A.C.A., Instructor in Clinical Medicine

ASSOCIATION OF MILITARY SURGEONS

The 1950 Convention of The Association of Military Surgeons of the United States was held November 9-11 at the Hotel Statler in New York City. Appropriate to the times, the programs dealt with civil defense, the defense role of the physician, aviation medicine, rehabilitation, military medicine, surgery, sanitation, and discussions on the use of the newest therapeutic and prophylactic agents in emergency conditions. Norvin C. Kiefer, M.D., F.A.C.A., of Bethesda, Maryland, spoke on Civil Defense Planning.

OHIO VALLEY SOCIETY

At the Ohio Valley Allergy Society meeting, held at the Seneca Hotel on October 7 and 8, new officers were elected. C. B. Bohner, M.D., F.A.C.A., Indianapolis, Indiana, was elected president; S. William Simon, M.D., F.A.C.A., Dayton, Ohio, is president-elect; and D. J. Parsons, M.D., F.A.C.A., Springfield, Ohio, was re-elected secretary-treasurer. Members of the College who presented papers are Dr. William Mount, Crawfordsville, Indiana, and Dr. John Martin of Columbus, Ohio.

COURSE ON ALLERGIC DISEASES

The New School for Social Research, 66 West 12th Street, New York City, announces a course of four lectures by Arthur F. Coca, M.D., F.A.C.A., covering the causes, the diagnosis, and the prevention of allergic diseases. New methods of

NEWS ITEMS

diagnosis and treatment will be discussed and illustrated. A demonstration of the pulse-dietary technique will be extended to all those attending the course. Dates of the lectures are January 23, 24, 30, and 31, 1951, at 8:30 P.M.

BRAZILIAN INSTITUTE FOR THE HISTORY OF MEDICINE

At a meeting of the Brazilian Institute for the History of Medicine at the General Polyclinic of Rio de Janeiro on July 19, two members of the Bahian Institute of the History of Medicine presented historical papers: Professor Alberto Silva and Professor Jose Lima. Dr. Involino de Vasconcellos presided at the meeting. Volume I, Number 2, of the official organ of the society, *Brazilian Review of the History of Medicine*, is circulating. Members were reminded of the First Brazilian Congress on the History of Medicine to be held in July of 1951.

The birthday of Oswaldo Cruz was celebrated by the institute on August 4 with an oration on yellow fever by Dr. Carlos da Silva Araujo.

AMERICAN ACADEMY OF DERMATOLOGY AND SYPHILIOLOGY

The ninth annual meeting of the American Academy of Dermatology and Syphilology was held in Chicago, December 2 through December 7, 1950. Special courses in histopathology and mycology were presented, December 2 and 3, at the Medical Schools of the University of Illinois and Northwestern University. Special courses in x-ray and radium therapy, bacteriology of the skin, anatomy and embryology of the skin, and special problems in dermatohistopathology were held at the Palmer House. Extensive scientific and technical exhibits were set up in connection with the meeting.

RED CROSS NATIONAL BLOOD PROGRAM

Dr. Russell Landram Haden, medical educator, author, and recently head of the Department of Medicine at the Cleveland (Ohio) Clinic, has been appointed medical director of the Red Cross National Blood Program, Gen. George C. Marshall, the organization's president, has announced. Doctor Haden will direct the medical aspects of the blood program as it is expanded to provide blood, plasma, and other derivatives for the nation's hospitals and for military and civil defense needs.

ALLERGIST WANTED

The director of a large hospital serving a community of over 200,000 people, is seeking a full-time allergist. Further information may be obtained from The American College of Allergists, 423 La Salle Medical Bldg., Minneapolis 2, Minn.

Since the appearance of Dr. Ira R. Morrison's article entitled "An Instrument Devised to Produce Painless Scratches" in the last issue of the ANNALS, many requests have been received for information as to where the instrument may be purchased. Doctor Morrison informs us, in reply to our inquiry, that the commercial name for the device is Micrometer Scratcher. The instruments are now being made by hand in a local machine shop. At present, the price is \$22.50. The response he has received since publication of the article, however, has led him to believe that it will be necessary to produce them on a production basis in the near future. At present, the instruments may be ordered directly through Doctor Morrison, Suite 11, Blair Bldg., Atchison, Kansas.

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